DA/8

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent 5,604,213

BARRIE et al. Atty. Ref.: 604-848; Confirmation No. 4753

Appl. No. 08/315,882 TC/A.U. 1202; Issued: February 18, 1997

Filed: September 30, 1994 Examiner: Bottino, A.

For: 17-SUBSTITUTED STEROIDS USEFUL IN CANCER TREATMENT

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June 22, 2011

Mail Stop Patent Extension
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

APPLICATION FOR EXTENSION OF PATENT TERM (37 C.F.R. § 1.740)

Pursuant to 35 U.S.C. §156(d) and 37 C.F.R. §1.740, BTG International Ltd. ("Applicant") as Assignee and patent owner of the above-captioned patent, hereby petitions for extension of U.S. Patent No. 5,604,213 (the '213 Patent). In support of such Petition, Applicant provides the following information:

I. SIGNATURE REQUIREMENTS (37 C.F.R. §1.730)

A. IDENTIFICATION OF PERSON(S) SUBMITTING THE APPLICATION

I, Leonard C. Mitchard, represent that I am a registered practitioner (Registration No. 29,009) appointed by the patent owner of record.

B. RECORDAL OF ASSIGNMENT IN PTO

British Technology Group Ltd., a corporation organized under the laws of England, having its principal office and place of business in London, England, now by change of name (recorded on November 15, 2010, at Reel 025364, Frame 0584), BTG International Ltd. (Applicant), is the owner of the entire right, title and interest in and to U.S. Patent 5,604,213 (the '213 Patent) granted to Susan Elaine BARRIE, Gerard Andrew POTTER, Michael JARMAN and Ian Robert HARDCASTLE, by reason of an assignment to Applicant recorded in the United States Patent & Trademark Office on September 30, 1994 at Reel 007172, Frame 0859.

C. PROOF OF AUTHORIZATION OF SIGNATORY TO ACT ON BEHALF OF THE PATENT OWNER

Attached as **Exhibit 1** is a Power of Attorney establishing authorization of Leonard C. Mitchard to act on behalf of the patent owner.

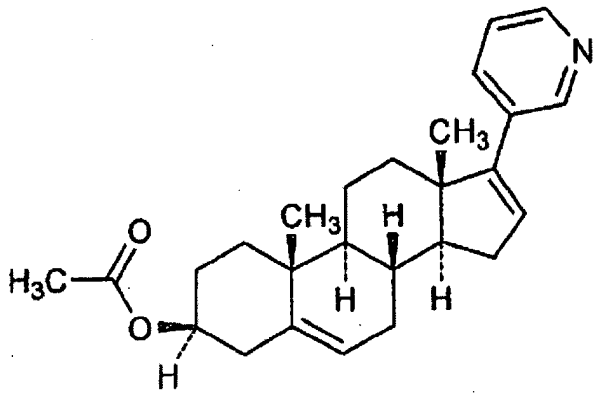
II. APPLICATION REQUIREMENTS (37 C.F.R. §1.740)

A. IDENTIFICATION OF APPROVED PRODUCT (1.740(a)(1))

The United States Food and Drug Administration ("FDA") has approved New Drug Application ("NDA") No. 202379 for ZYTIGA™ (abiraterone acetate). The active ingredient of ZYTIGA is abiraterone acetate. A copy of the approved labeling is attached hereto as **Exhibit 2**.

The chemical names for abiraterone acetate are 3β-acetoxy-17-(3-pyridyl)androsta-5,16-diene and (3β)-17-(3-pyridinyl)androsta-5,16-dien-3-yl-acetate and the molecular formula is $C_{26}H_{33}NO_2$.

Abiraterone acetate has the following structural formula:



Each tablet of ZYTIGA contains 250 mg abiraterone acetate.

ZYTIGA in combination with prednisone is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC) who have received prior chemotherapy containing docetaxel.

B. IDENTIFICATION OF THE FEDERAL STATUTE UNDER WHICH REGULATORY REVIEW OCCURRED (1.740(a)(2))

Regulatory review for this product occurred under the Federal Food Drug & Cosmetic Act ("FDC Act") §505(b), 21 U.S.C. §355 (new drugs).

C. DATE OF APPROVAL (1.740(a)(3))

The FDA approved No. 202379 for ZYTIGA for commercial marketing or use under §505 of the FDC Act on April 28, 2011.

D. IDENTIFICATION OF ACTIVE INGREDIENTS AND PREVIOUS APPROVAL INFORMATION (1.740(a)(4))

ZYTIGA™ is a human drug product, the sole active ingredient of which is abiraterone acetate. Neither abiraterone acetate, nor any other salt or ester thereof, has been previously approved, alone or in combination, for commercial marketing or use under the Food, Drug & Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

E. TIMELY SUBMISSION OF APPLICATION (60 DAYS) (1.740(a)(5))

This application is being submitted within the sixty-day time period permitted for submission pursuant to 37 C.F.R. §1.720(f). The last date this application may be submitted is June 27, 2011.

F. IDENTIFICATION OF PATENT (1.740(a)(6), (7), (8))

Name of the Inventors:	Susan E. Barrie Michael Jarman Gerard A. Potter Ian R. Hardcastle
Patent No.	5,604,213
Date of Issue:	February 18, 1997
Date of Original Expiration:	February 18, 2014

A copy of the patent, including the entire specification (with claims), drawings, and Certificate of Correction is attached as **Exhibit 3**.

A copy of the U.S. Patent & Trademark Office Maintenance Fee Statement is attached as **Exhibit 4**.

G. IDENTIFICATION OF CLAIMS READING ON THE APPROVED PRODUCT (1.740(a)(9))

The '213 Patent claims the active ingredient of the approved product which is abiraterone acetate. The '213 Patent includes 22 claims. Claims 1, 3-5, 7-12, 14, 15 and 22 read on the approved product. Claims 2, 16, 18, 19, 20 and 21 read on the approved method of using the approved product.

The manner in which at least one claim which reads on the approved product (Claim 8) and the method of using the approved product (Claim 21) is demonstrated below:

Claim 8 reads: "3β-Acetoxy-17-(3-pyridyl)androsta-5,16-diene." The chemical name of the active ingredient in ZYTIGA, the approved product, is 3β-acetoxy-17-(3-pyridyl)androsta-5,16-diene. Thus, claim 8 reads on the approved product.

Claim 21 depends from claim 2 and thus incorporates all the limitations thereof. Claim 2 reads, in part: "A method of treating an androgen-dependent or estrogen-dependent disorder which comprises administering to a patient in a therapeutically effective dose a compound of the formula (1) . . ." According to the '213 Patent, the invention includes "a method of treating androgen- and oestrogen-dependent disorders, especially tumours . . . The preferred use is in treating prostatic cancer." The '213 Patent, col. 10, lines 47-56. Claim 16 depends from claim 2 and states "A method according to claim 2 wherein the patient has prostatic cancer." Thus, prostatic cancer is an androgen or estrogen-dependent disorder, according to the '213 Patent.

Claim 21 reads: "A method according to claim 2 wherein the compound is 3β-acetoxy-17-(3-pyridyl)androsta-5,16-diene." Thus, claim 21 is directed to: A method of treating an androgen-dependent or estrogen-dependent disorder [such as prostatic cancer] which comprises administering to a patient in a therapeutically effective dose 3β-acetoxy-17-(3-pyridyl)androsta-5,16-diene.

ZYTIGA is indicated for the treatment of a particular population of patients with a particular type of prostatic cancer, metastatic castration-resistant prostate cancer (CRPC). As stated above, the chemical name of the active ingredient in ZYTIGA is 3β-acetoxy-17-(3-pyridyl)androsta-5,16-diene. Claim 21 reads on a method of treating prostatic cancer with 3β-acetoxy-17-(3-pyridyl)androsta-5,16-diene. Thus, claim 21 reads on the method of using the approved product.

H. RELEVANT DATES AND INFORMATION (1.740(a)(10))

The '213 Patent claims a human drug.

The effective date of the investigational new drug (IND) application was January 28, 2006 and the IND No. is 071023.

The new drug application (NDA) was initially submitted on December 20, 2010. The NDA No. is 202379.

The NDA was approved on April 28, 2011.

I. DESCRIPTION OF SIGNIFICANT ACTIVITIES OF APPLICANT DURING REGULATORY REVIEW (1.740(a)(11))

Tables 1 and 2 below are a "DESCRIPTION OF SIGNIFICANT ACTIVITIES OF APPLICANT DURING REGULATORY REVIEW" that provides a description of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.

Table 1. ZYTIGA IND 071023 SUBMISSION LOG

FDA Submission Date	Serial No.	Type of Submission
19-Dec-05	0000	Initial IND
8-Feb-06	0001	Response to FDA request
23-Feb-06	0002	Information Amendment: Chemistry/Microbiology
19-Apr-06	0003	Information Amendment: Pharmacology/toxicology
23-Jun-06	0004	Other
23-Jun-06	0005	Protocol Amendment: Change in Protocol
23-Jun-06		Protocol Amendment: New Investigator
23-Oct-06	0006	Protocol Amendment: Change in Protocol
29-Nov-06	0007	Protocol Amendment: Change in Protocol
29-Nov-06		Protocol Amendment: New Investigator
29-Nov-06		Information Amendment: Chemistry/Microbiology
29-Nov-06		Information Amendment: Clinical
14-Dec-06	0008	IND Amendment: Safety Report
14-Dec-06		Information Amendment: Chemistry/Microbiology
22-Dec-06	0009	IND Amendment: Safety Report
29-Jan-07	0010	IND Amendment: Safety Report
29-Jan-07		IND Amendment: Safety Report
15-Feb-07	0011	Protocol Amendment: Change in Protocol
28-Feb-07	0012	Protocol Amendment: Change in Protocol
15-Mar-07	0013	Protocol Amendment: New Protocol
		Protocol Amendment: Change in Protocol
23-Mar-07	0014	IND Amendment: Safety Report
30-Mar-07	0015	IND Amendment: Safety Report
26-Apr-07	0016	IND Amendment: Safety Report
19-Apr-07	0017	IND Amendment: Safety Report
7-May-07	0018	Protocol Amendment: New Protocol
9-May-07	0019	Information Amendment: Clinical
8-May-07	0020	IND Amendment: Safety Report
15-May-07	0021	IND Amendment: Safety Report
15-May-07		IND Amendment: Safety Report
24-May-07	0022	Protocol Amendment: Change in Protocol
31-May-07	0023	Protocol Amendment: Change in Protocol
12-Jun-07	0024	General Correspondence
29-Jun-07	0025	Protocol Amendment: Change in Protocol
10-Aug-07	0026	IND Amendment: Safety Report
27-Aug-07	0027	General Correspondence
31-Aug-07	0028	IND Amendment: Safety Report

FDA Submission Date	Serial No.	Type of Submission
31-Aug-07	0029	IND Amendment: Safety Report
14-Sep-07	0030	Information Amendment: Pharmacology/toxicology
14-Sep-07	0031	IND Amendment: Safety Report
21-Sep-07	0032	IND Amendment: Safety Report
24-Sep-07	0033	Protocol Amendment: New Protocol
5-Oct-07	0034	IND Amendment: Safety Report
8-Oct-07	0035	Response to FDA request
29-Oct-07	0036	IND Amendment: Safety Report
31-Oct-07	0037	Response to FDA request
31-Oct-07	0038	IND Amendment: Safety Report
5-Nov-07	0039	Other
16-Nov-07	0040	Protocol Amendment: Change in Protocol
19-Nov-07	0041	Annual Report
20-Nov-07	0042	Other
4-Dec-07	0043	IND Amendment: Safety Report
17-Dec-07	0044	General Correspondence
21-Dec-07	0045	Other
10-Jan-08	0046	Other
29-Jan-08	0047	Information Amendment: Chemistry/Microbiology
5-Feb-08	0048	General Correspondence
8-Feb-08	0049	Other
12-Feb-08	0050	IND Amendment: Safety Report
15-Feb-08	0051	General Correspondence
15-Feb-08	0052	Information Amendment: Non-Clinical
25-Feb-08	0053	Other
6-Mar-08	0054	Information Amendment: Clinical
6-Mar-08	0055	Information Amendment: Clinical
21-Mar-08	0056	Information Amendment: Chemistry/Microbiology
25-Mar-08	0057	IND Amendment: Safety Report
26-Mar-08	0058	IND Amendment: Safety Report
2-Apr-08	0059	Protocol Amendment: New Protocol
4-Apr-08	0060	Protocol Amendment: Change in Protocol
10-Apr-08	0061	IND Amendment: Safety Report
10-Apr-08		IND Amendment: Safety Report
17-Apr-08	0062	IND Amendment: Safety Report
21-Apr-08	0063	Other
22-Apr-08	0064	IND Amendment: Safety Report
23-Apr-08	0065	IND Amendment: Safety Report
25-Apr-08	0066	IND Amendment: Safety Report
30-Apr-08	0067	Protocol Amendment: Change in Protocol
2-May-08	0068	Protocol Amendment: New Protocol
2-May-08	0069	Protocol Amendment: Change in Protocol
2-May-08	0070	Protocol Amendment: Change in Protocol
6-May-08	0071	Protocol Amendment: New Investigator
6-May-08	0072	IND Amendment: Safety Report
13-May-08	0073	Other
16-May-08	0074	IND Amendment: Safety Report
16-May-08	0075	IND Amendment: Safety Report
22-May-08	0076	IND Amendment: Safety Report
30-May-08	0077	IND Amendment: Safety Report

FDA Submission Date	Serial No.	Type of Submission
2-Jun-08	0078	Protocol Amendment: New Investigator
16-Jun-08	0079	Response to FDA request
17-Jun-08	0080	IND Amendment: Safety Report
17-Jun-08	0081	IND Amendment: Safety Report
23-Jun-08	0082	ERRATA: IND Safety Report SN0081
30-Jun-08	0083	Information Amendment: Clinical
1-Jul-08	0084	IND Amendment: Safety Report
1-Jul-08	0085	Protocol Amendment: New Investigator
1-Jul-08	0086	Other
1-Jul-08	0087	IND Amendment: Safety Report
17-Jul-08	0088	IND Amendment: Safety Report
18-Jul-08	0089	ERRATA: IND Safety Report SN0050
18-Jul-08	0090	Protocol Amendment: New Protocol
18-Jul-08	0091	Protocol Amendment: Change in Protocol
22-Jul-08	0092	ERRATA: IND Amendment 0091
23-Jul-08	0093	ERRATA: IND Safety Report SN0077
24-Jul-08	0094	IND Amendment: Safety Report
25-Jul-08	0095	IND Amendment: Safety Report
25-Jul-08	0096	ERRATA: IND Safety Report SN0077
28-Jul-08	0097	IND Amendment: Safety Report
29-Jul-08	0098	IND Amendment: Safety Report
1-Aug-08	0099	Protocol Amendment: Change in Protocol
1-Aug-08	0100	Protocol Amendment: New Investigator
1-Aug-08	0101	Other
8-Aug-08	0102	IND Amendment: Safety Report
12-Aug-08	0103	IND Amendment: Safety Report
15-Aug-08	0104	Protocol Amendment: Change in Protocol
15-Aug-08	0105	Information Amendment: ERRATA 0083
19-Aug-08	0106	IND Amendment: Safety Report
19-Aug-08	0107	IND Amendment: Safety Report
19-Aug-08	0108	Protocol Amendment: Change in Protocol
19-Aug-08	0109	IND Amendment: Safety Report
19-Aug-08	0110	Other
21-Aug-08	0111	IND Amendment: Safety Report
21-Aug-08	0112	IND Amendment: Safety Report
22-Aug-08	0113	IND Amendment: Safety Report
22-Aug-08	0114	IND Amendment: Safety Report
29-Aug-08	0115	IND Amendment: Safety Report
29-Aug-08	0116	Protocol Amendment: Change in Protocol
29-Aug-08	0117	IND Amendment: Safety Report
2-Sep-08	0118	ERRATA: Safety Report 0103
2-Sep-08	0119	IND Amendment: Safety Report
3-Sep-08	0120	IND Amendment: Safety Report
3-Sep-08	0121	Protocol Amendment: New Investigator
5-Sep-08	0122	IND Amendment: Safety Report
6-Sep-08	0123	IND Amendment: Safety Report
9-Sep-08	0124	IND Amendment: Safety Report
11-Sep-08	0125	Information Amendment: Pharmacology/toxicology
11-Sep-08	0126	IND Amendment: Safety Report
11-Sep-08	0127	IND Amendment: Safety Report

FDA Submission Date	Serial No.	Type of Submission
17-Sep-08	0128	IND Amendment: Safety Report
17-Sep-08	0129	IND Amendment: Safety Report
12-Sep-08	0130	Response to FDA Comments - SN0110
19-Sep-08	0131	IND Amendment: Safety Report
20-Sep-08	0132	IND Amendment: Safety Report
26-Sep-08	0133	IND Amendment: Safety Report
30-Sep-08	0134	Other
1-Oct-08	0135	IND Amendment: Safety Report
7-Oct-08	0136	IND Amendment: Safety Report
7-Oct-08	0137	Protocol Amendment: New Investigator
7-Oct-08	0138	Information Amendment: Pharmacology/toxicology
8-Oct-08	0139	Other
10-Oct-08	0140	IND Amendment: Safety Report
13-Oct-08	0141	IND Amendment: Safety Report
14-Oct-08	0142	IND Amendment: Safety Report
14-Oct-08	0143	IND Amendment: Safety Report
15-Oct-08	0144	IND Amendment: Safety Report
16-Oct-08	0145	Information Amendment: Pharmacology/toxicology
16-Oct-08	0146	Information Amendment: Pharmacology/toxicology
23-Oct-08	0147	Protocol Amendment: Change in Protocol
23-Oct-08	0148	IND Amendment: Safety Report
24-Oct-08	0149	Dear Investigator Letter
24-Oct-08	0150	IND Amendment: Safety Report
30-Oct-08	0151	IND Amendment: Safety Report
5-Nov-08	0152	Response to FDA request
4-Nov-08	0153	Protocol Amendment: New Investigator
4-Nov-08	0154	IND Amendment: Safety Report
5-Nov-08	0155	Protocol Amendment: Change in Protocol
5-Nov-08	0156	IND Amendment: Safety Report
5-Nov-08	0157	Information Amendment: Pharmacology/toxicology
12-Nov-08	0158	IND Amendment: Safety Report
14-Nov-08	0159	IND Amendment: Safety Report
14-Nov-08	0160	IND Amendment: Safety Report
14-Nov-08	0161	General Correspondence
14-Nov-08	0162	Protocol Amendment: New Protocol
18-Nov-08	0163	IND Amendment: Safety Report
18-Nov-08	0164	IND Amendment: Safety Report
19-Nov-08	0165	IND Amendment: Safety Report
19-Nov-08	0166	Other
21-Nov-08	0167	IND Amendment: Safety Report
21-Nov-08	0168	Annual Report
22-Nov-08	0169	IND Amendment: Safety Report
24-Nov-08	0170	IND Amendment: Safety Report
25-Nov-08	0171	IND Amendment: Safety Report
25-Nov-08	0172	IND Amendment: Safety Report
26-Nov-08	0173	IND Amendment: Safety Report
26-Nov-08	0174	IND Amendment: Safety Report
26-Nov-08	0175	IND Amendment: Safety Report
1-Dec-08	0176	Other
27-Nov-08	0177	IND Amendment: Safety Report

FDA Submission Date	Serial No.	Type of Submission
2-Dec-08	0178	IND Amendment: Safety Report
3-Dec-08	0179	ERRATA: IND Safety Report SN0077
5-Dec-08	0180	Protocol Amendment: New Investigator
5-Dec-08	0181	Protocol Amendment: Change in Protocol
9-Dec-08	0182	IND Amendment: Safety Report
9-Dec-08	0183	IND Amendment: Safety Report
9-Dec-08	0184	IND Amendment: Safety Report
10-Dec-08	0185	IND Amendment: Safety Report
10-Dec-08	0186	IND Amendment: Safety Report
10-Dec-08	0187	IND Amendment: Safety Report
11-Dec-08	0188	IND Amendment: Safety Report
11-Dec-08	0189	IND Amendment: Safety Report
11-Dec-08	0190	IND Amendment: Safety Report
15-Dec-08	0191	IND Amendment: Safety Report
15-Dec-08	0192	Information Amendment: Chemistry/Microbiology
17-Dec-08	0193	IND Amendment: Safety Report
17-Dec-08	0194	IND Amendment: Safety Report
18-Dec-08	0195	IND Amendment: Safety Report
19-Dec-08	0196	IND Amendment: Safety Report
19-Dec-08	0197	IND Amendment: Safety Report
22-Dec-08	0198	IND Amendment: Safety Report
22-Dec-08	0199	Other
24-Dec-08	0200	IND Amendment: Safety Report
24-Dec-08	0201	IND Amendment: Safety Report
24-Dec-08	0202	IND Amendment: Safety Report
24-Dec-08	0203	IND Amendment: Safety Report
30-Dec-08	0204	IND Amendment: Safety Report
23-Dec-08	0205	IND Amendment: Safety Report
30-Dec-08	0206	IND Amendment: Safety Report
31-Dec-08	0207	IND Amendment: Safety Report
31-Dec-08	0208	IND Amendment: Safety Report
31-Dec-08	0209	IND Amendment: Safety Report
6-Jan-09	0210	Dear Investigator Letter
31-Dec-08	0211	IND Amendment: Safety Report
6-Jan-09	0212	IND Amendment: Safety Report
6-Jan-09	0213	IND Amendment: Safety Report
7-Jan-09	0214	IND Amendment: Safety Report
7-Jan-09	0215	IND Amendment: Safety Report
7-Jan-09	0216	IND Amendment: Safety Report
9-Jan-09	0217	Protocol Amendment: New Investigator
9-Jan-09	0218	Administrative Amendment
13-Jan-09	0219	IND Amendment: Safety Report
13-Jan-09	0220	IND Amendment: Safety Report
13-Jan-09	0221	IND Amendment: Safety Report
13-Jan-09	0222	IND Amendment: Safety Report
13-Jan-09	0223	IND Amendment: Safety Report
13-Jan-09	0224	Other
14-Jan-09	0225	IND Amendment: Safety Report
13-Jan-09	0226	IND Amendment: Safety Report
13-Jan-09	0227	IND Amendment: Safety Report

FDA Submission Date	Serial No.	Type of Submission
13-Jan-09	0228	IND Amendment: Safety Report
13-Jan-09	0229	IND Amendment: Safety Report
14-Jan-09	0230	IND Amendment: Safety Report
14-Jan-09	0231	IND Amendment: Safety Report
14-Jan-09	0232	IND Amendment: Safety Report
16-Jan-09	0233	IND Amendment: Safety Report
16-Jan-09	0234	IND Amendment: Safety Report
19-Jan-09	0235	IND Amendment: Safety Report
20-Jan-09	0236	IND Amendment: Safety Report
20-Jan-09	0237	Protocol Amendment: Change in Protocol
20-Jan-09	0238	Protocol Amendment: Change in Protocol
20-Jan-09	0239	IND Amendment: Safety Report
21-Jan-09	0240	IND Amendment: Safety Report
21-Jan-09	0241	IND Amendment: Safety Report
21-Jan-09	0242	IND Amendment: Safety Report
22-Jan-09	0243	IND Amendment: Safety Report
23-Jan-09	0244	ERRATA: IND Safety Report SN0213
23-Jan-09	0245	IND Amendment: Safety Report
23-Jan-09	0246	IND Amendment: Safety Report
23-Jan-09	0247	IND Amendment: Safety Report
26-Jan-09	0248	IND Amendment: Safety Report
26-Jan-09	0249	Other
27-Jan-09	0250	IND Amendment: Safety Report
27-Jan-09	0251	IND Amendment: Safety Report
28-Jan-09	0252	IND Amendment: Safety Report
29-Jan-09	0253	IND Amendment: Safety Report
29-Jan-09	0254	IND Amendment: Safety Report
30-Jan-09	0255	IND Amendment: Safety Report
30-Jan-09	0256	IND Amendment: Safety Report
31-Jan-09	0257	IND Amendment: Safety Report
30-Jan-09	0258	Other
2-Feb-09	0259	IND Amendment: Safety Report
2-Feb-09	0260	Protocol Amendment: New Protocol
2-Feb-09	0261	Protocol Amendment: New Investigator
2-Feb-09	0262	Information Amendment: Clinical
3-Feb-09	0263	IND Amendment: Safety Report
3-Feb-09	0264	Protocol Amendment: Change in Protocol
4-Feb-09	0265	IND Amendment: Safety Report
4-Feb-09	0266	IND Amendment: Safety Report
5-Feb-09	0267	IND Amendment: Safety Report
5-Feb-09	0268	IND Amendment: Safety Report
6-Feb-09	0269	IND Amendment: Safety Report
6-Feb-09	0270	IND Amendment: Safety Report
9-Feb-09	0271	IND Amendment: Safety Report
10-Feb-09	0272	IND Amendment: Safety Report
11-Feb-09	0273	IND Amendment: Safety Report
11-Feb-09	0274	IND Amendment: Safety Report
11-Feb-09	0275	IND Amendment: Safety Report
16-Feb-09	0276	IND Amendment: Safety Report
17-Feb-09	0277	IND Amendment: Safety Report

FDA Submission Date	Serial No.	Type of Submission
18-Feb-09	0278	IND Amendment: Safety Report
18-Feb-09	0279	General Correspondence
19-Feb-09	0280	IND Amendment: Safety Report
19-Feb-09	0281	IND Amendment: Safety Report
20-Feb-09	0282	IND Amendment: Safety Report
24-Feb-09	0283	IND Amendment: Safety Report
24-Feb-09	0284	IND Amendment: Safety Report
25-Feb-09	0285	IND Amendment: Safety Report
26-Feb-09	0286	Protocol Amendment: New Protocol
26-Feb-09	0287	Protocol Amendment: Change in Protocol
26-Feb-09	0288	IND Amendment: Safety Report
2-Mar-09	0289	IND Amendment: Safety Report
5-Mar-09	0290	IND Amendment: Safety Report
5-Mar-09	0291	IND Amendment: Safety Report
9-Mar-09	0292	IND Amendment: Safety Report
10-Mar-09	0293	IND Amendment: Safety Report
11-Mar-09	0294	Protocol Amendment: New Investigator
12-Mar-09	0295	IND Amendment: Safety Report
13-Mar-09	0296	IND Amendment: Safety Report
16-Mar-09	0297	Protocol Amendment: Change in Protocol
18-Mar-09	0298	IND Amendment: Safety Report
20-Mar-09	0299	IND Amendment: Safety Report
24-Mar-09	0300	Information Amendment: Chemistry/Microbiology
24-Mar-09	0301	IND Amendment: Safety Report
25-Mar-09	0302	IND Amendment: Safety Report
26-Mar-09	0303	IND Amendment: Safety Report
27-Mar-09	0304	Protocol Amendment: Change in Protocol
30-Mar-09	0305	Protocol Amendment: Change in Protocol
27-Mar-09	0306	IND Amendment: Safety Report
30-Mar-09	0307	IND Amendment: Safety Report
1-Apr-09	0308	IND Amendment: Safety Report
1-Apr-09	0309	Protocol Amendment: New Investigator
3-Apr-09	0310	Other
3-Apr-09	0311	Protocol Amendment: Change in Protocol
3-Apr-09	0312	IND Amendment: Safety Report
6-Apr-09	0313	Protocol Amendment: Change in Protocol
6-Apr-09	0314	Protocol Amendment: Change in Protocol
6-Apr-09	0315	Protocol Amendment: Change in Protocol
6-Apr-09	0316	IND Amendment: Safety Report
7-Apr-09	0317	Protocol Amendment: New Protocol
7-Apr-09	0318	Information Amendment: Clinical (Errata)
8-Apr-09	0319	IND Amendment: Safety Report
9-Apr-09	0320	IND Amendment: Safety Report
10-Apr-09	0321	IND Amendment: Safety Report
13-Apr-09	0322	IND Amendment: Safety Report
14-Apr-09	0323	IND Amendment: Safety Report
14-Apr-09	0324	Protocol Amendment: New Investigator
16-Apr-09	0325	IND Amendment: Safety Report
21-Apr-09	0326	IND Amendment: Safety Report
22-Apr-09	0327	General Correspondence

FDA Submission Date	Serial No.	Type of Submission
22-Apr-09	0328	IND Amendment: Safety Report
23-Apr-09	0329	IND Amendment: Safety Report
24-Apr-09	0330	Other
24-Apr-09	0331	Information Amendment: Pharmacology/Toxicology
28-Apr-09	0332	IND Amendment: Safety Report
28-Apr-09	0333	Protocol Amendment: New Investigator
28-Apr-09	0334	IND Amendment: Safety Report
29-Apr-09	0335	Protocol Amendment: New Investigator
1-May-09	0336	IND Amendment: Safety Report
1-May-09	0337	IND Amendment: Safety Report
14-May-09	0338	Other
12-May-09	0339	IND Amendment: Safety Report
12-May-09	0340	Protocol Amendment: New Investigator
15-May-09	0341	IND Amendment: Safety Report
15-May-09	0342	IND Amendment: Safety Report
19-May-09	0343	IND Amendment: Safety Report
19-May-09	0344	Other
19-May-09	0345	IND Amendment: Safety Report
1-Jun-10	0346	Protocol Amendment: Change in Protocol
22-May-10	0347	IND Amendment: Safety Report
26-May-10	0348	Protocol Amendment: New Protocol
27-May-09	0349	IND Amendment: Safety Report
28-May-09	0350	IND Amendment: Safety Report
29-May-09	0351	Protocol Amendment: New Investigator
3-Jun-09	0352	Information Amendment: Chemistry/Microbiology
29-Jun-09	0353	General Correspondence
2-Jun-09	0354	IND Amendment: Safety Report
3-Jun-09	0355	Other
4-Jun-09	0356	IND Amendment: Safety Report
4-Jun-09	0357	IND Amendment: Safety Report
9-Jun-09	0358	IND Amendment: Safety Report
10-Jun-09	0359	Other
16-Jun-09	0360	IND Amendment: Safety Report
16-Jun-09	0361	Protocol Amendment: New Investigator
18-Jun-09	0362	Protocol Amendment: New Investigator
19-Jun-09	0363	IND Amendment: Safety Report
23-Jun-09	0364	Protocol Amendment: New Investigator
24-Jun-09	0365	IND Amendment: Safety Report
26-Jun-09	0366	IND Amendment: Safety Report
30-Jun-09	0367	IND Amendment: Safety Report
9-Jul-10	0368	Protocol Amendment: New Investigator
1-Jul-09	0369	Protocol Amendment: New Investigator
1-Jul-09	0370	IND Amendment: Safety Report
7-Jul-09	0371	IND Amendment: Safety Report
8-Jul-09	0372	IND Amendment: Safety Report
14-Jul-09	0373	IND Amendment: Safety Report
21-Jul-09	0374	IND Amendment: Safety Report
21-Jul-09	0375	IND Amendment: Safety Report
24-Jul-09	0376	Other
29-Jul-09	0377	IND Amendment: Safety Report

FDA Submission Date	Serial No.	Type of Submission
29-Jul-09	0378	Protocol Amendment: New Investigator
30-Jul-09	0379	Protocol Amendment: New Protocol
30-Jul-09	0380	Protocol Amendment: New Protocol
30-Jul-09	0381	IND Amendment: Safety Report
30-Jul-09	0382	Protocol Amendment: New Investigator
31-Jul-09	0383	Protocol Amendment: New Protocol
4-Aug-09	0384	IND Amendment: Safety Report
7-Aug-09	0385	IND Amendment: Safety Report
11-Aug-09	0386	IND Amendment: Safety Report
14-Aug-09	0387	IND Amendment: Safety Report
14-Aug-09	0388	Information Amendment: Pharmacology/Toxicology
18-Aug-09	0389	IND Amendment: Safety Report
19-Aug-09	0390	IND Amendment: Safety Report
21-Aug-09	0391	IND Amendment: Safety Report
21-Aug-09	0392	Protocol Amendment: Change in Protocol
24-Aug-09	0393	Protocol Amendment: New Protocol
24-Aug-09	0394	Protocol Amendment: New Investigator
25-Aug-09	0395	IND Amendment: Safety Report
27-Aug-09	0396	IND Amendment: Safety Report
31-Aug-09	0397	General Correspondence
1-Sep-09	0398	IND Amendment: Safety Report
1-Sep-09	0399	IND Amendment: Safety Report
1-Sep-09	0400	Protocol Amendment: New Investigator
3-Sep-09	0401	IND Amendment: Safety Report
2-Sep-09	0402	Protocol Amendment: New Investigator
1-Sep-09	0403	IND Amendment: Safety Report
8-Sep-09	0404	IND Amendment: Safety Report
10-Sep-09	0405	Protocol Amendment: New Protocol
10-Sep-09	0406	IND Amendment: Safety Report
11-Sep-09	0407	IND Amendment: Safety Report
14-Sep-09	0408	IND Amendment: Safety Report
14-Sep-09	0409	IND Amendment: Safety Report
16-Sep-09	0410	Protocol Amendment: New Investigator
16-Sep-09	0411	Protocol Amendment: New Investigator
17-Sep-09	0412	IND Amendment: Safety Report
17-Sep-09	0413	IND Amendment: Safety Report
22-Sep-09	0414	Protocol Amendment: New Investigator
22-Sep-09	0415	IND Amendment: Safety Report
22-Sep-09	0416	Protocol Amendment: New Investigator
5-Oct-09	0417	Protocol Amendment: Change in Protocol
28-Sep-09	0418	IND Amendment: Safety Report
28-Sep-09	0419	Protocol Amendment: Change in Protocol
30-Sep-09	0420	Protocol Amendment: New Investigator
29-Sep-09	0421	IND Amendment: Safety Report
29-Sep-09	0422	IND Amendment: Safety Report
2-Oct-09	0423	Information Amendment: Chemistry/Microbiology
5-Oct-09	0424	Protocol Amendment: New Investigator
5-Oct-09	0425	IND Amendment: Safety Report
6-Oct-09	0426	Protocol Amendment: New Investigator
5-Oct-09	0427	IND Amendment: Safety Report

FDA Submission Date	Serial No.	Type of Submission
6-Oct-09	0428	IND Amendment: Safety Report
8-Oct-09	0429	Protocol Amendment: New Investigator
7-Oct-09	0430	IND Amendment: Safety Report
7-Oct-09	0431	IND Amendment: Safety Report
9-Oct-09	0432	IND Amendment: Safety Report
13-Oct-09	0433	IND Amendment: Safety Report
13-Oct-09	0434	IND Amendment: Safety Report
15-Oct-09	0435	IND Amendment: Safety Report
20-Oct-09	0435	IND Amendment: Safety Report
20-Oct-09	0436	IND Amendment: Safety Report
20-Oct-09	0437	IND Amendment: Safety Report
21-Oct-09	0438	Protocol Amendment: New Investigator
21-Oct-09	0439	Protocol Amendment: New Investigator
22-Oct-09	0440	IND Amendment: Safety Report
22-Oct-09	0441	IND Amendment: Safety Report
23-Oct-09	0442	Other
27-Oct-09	0443	IND Amendment: Safety Report
17-Nov-09	0444	Protocol Amendment: New Investigator
27-Oct-09	0445	IND Amendment: Safety Report
27-Oct-09	0446	IND Amendment: Safety Report
28-Oct-09	0447	Protocol Amendment: New Investigator
29-Oct-09	0448	Protocol Amendment: New Investigator
28-Oct-09	0449	Protocol Amendment: New Investigator
29-Oct-09	0450	Protocol Amendment: New Investigator
29-Oct-09	0451	IND Amendment: Safety Report
29-Oct-09	0452	IND Amendment: Safety Report
29-Oct-09	0453	IND Amendment: Safety Report
2-Nov-09	0454	eCTD Correction: Safety Report
3-Nov-09	0455	IND Amendment: Safety Report
3-Nov-09	0456	Protocol Amendment: New Investigator
4-Nov-09	0457	IND Amendment: Safety Report
5-Nov-09	0458	IND Amendment: Safety Report
4-Nov-09	0459	IND Amendment: Safety Report
5-Nov-09	0460	IND Amendment: Safety Report
9-Nov-09	0461	Protocol Amendment: New Protocol
9-Nov-09	0462	IND Amendment: Safety Report
10-Nov-09	0463	IND Amendment: Safety Report
11-Nov-09	0464	Protocol Amendment: New Investigator
11-Nov-09	0465	Protocol Amendment: New Investigator
11-Nov-09	0466	Protocol Amendment: New Investigator
11-Nov-09	0467	Protocol Amendment: New Investigator
11-Nov-09	0468	Protocol Amendment: New Investigator
12-Nov-09	0469	IND Amendment: Safety Report
20-Nov-09	0470	Protocol Amendment: New Investigator
17-Nov-09	0471	IND Amendment: Safety Report
19-Nov-09	0472	Annual Report
17-Nov-09	0473	Protocol Amendment: New Protocol
20-Nov-09	0474	IND Amendment: Safety Report
17-Nov-09	0475	IND Amendment: Safety Report
20-Nov-09	0476	IND Amendment: Safety Report

FDA Submission Date	Serial No.	Type of Submission
23-Nov-09	0477	IND Amendment: Safety Report
25-Nov-09	0478	IND Amendment: Safety Report
25-Nov-09	0479	Other
30-Nov-09	0480	IND Amendment: Safety Report
30-Nov-09	0481	IND Amendment: Safety Report
1-Dec-09	0482	IND Amendment: Safety Report
3-Dec-09	0483	IND Amendment: Safety Report
4-Dec-09	0484	Protocol Amendment: New Investigator
8-Dec-09	0485	IND Amendment: Safety Report
11-Dec-09	0486	Protocol Amendment: Change in Protocol
11-Dec-09	0487	General Correspondence
11-Dec-09	0488	IND Amendment: Safety Report
14-Dec-09	0489	IND Amendment: Safety Report
14-Dec-09	0490	IND Amendment: Safety Report
17-Dec-09	0491	IND Amendment: Safety Report
17-Dec-09	0492	IND Amendment: Safety Report
17-Dec-09	0493	IND Amendment: Safety Report
17-Dec-09	0494	IND Amendment: Safety Report
22-Dec-09	0495	IND Amendment: Safety Report
22-Dec-09	0496	Protocol Amendment: Change in Protocol
23-Dec-09	0497	Protocol Amendment: Change in Protocol
23-Dec-09	0498	IND Amendment: Safety Report
30-Dec-09	0499	Protocol Amendment: Change in Protocol
29-Dec-09	0500	IND Amendment: Safety Report
28-Dec-09	0501	IND Amendment: Safety Report
30-Dec-09	0502	Protocol Amendment: New Investigator
4-Jan-10	0503	Protocol Amendment: New Investigator
30-Dec-09	0504	IND Amendment: Safety Report
30-Dec-09	0505	IND Amendment: Safety Report
5-Jan-10	0506	IND Amendment: Safety Report
7-Jan-10	0507	IND Amendment: Safety Report
7-Jan-10	0508	IND Amendment: Safety Report
8-Jan-10	0509	IND Amendment: Safety Report
12-Jan-10	0510	Information Amendment: Pharmacology/Toxicology
14-Jan-10	0511	IND Amendment: Safety Report
12-Jan-10	0512	Protocol Amendment: New Investigator
14-Jan-10	0513	IND Amendment: Safety Report
14-Jan-10	0514	IND Amendment: Safety Report
14-Jan-10	0515	Information Amendment: Chemistry/Microbiology
14-Jan-10	0516	Protocol Amendment: New Protocol
20-Jan-10	0517	IND Amendment: Safety Report
25-Jan-10	0518	Information Amendment: Clinical
22-Jan-10	0519	IND Amendment: Safety Report
25-Jan-10	0520	IND Amendment: Safety Report
27-Jan-10	0521	Protocol Amendment: New Protocol
26-Jan-10	0522	IND Amendment: Safety Report
28-Jan-10	0523	IND Amendment: Safety Report
29-Jan-10	0524	Protocol Amendment: New Investigator
29-Jan-10	0525	IND Amendment: Safety Report
8-Feb-10	0526	General Correspondence

FDA Submission Date	Serial No.	Type of Submission
2-Feb-10	0527	IND Amendment: Safety Report
3-Feb-10	0528	IND Amendment: Safety Report
4-Feb-10	0529	IND Amendment: Safety Report
9-Feb-10	0530	IND Amendment: Safety Report
8-Feb-10	0531	IND Amendment: Safety Report
12-Feb-10	0532	IND Amendment: Safety Report
12-Feb-10	0533	IND Amendment: Safety Report
9-Feb-10	0534	IND Amendment: Safety Report
16-Feb-10	0535	IND Amendment: Safety Report
17-Feb-10	0536	IND Amendment: Safety Report
17-Feb-10	0537	IND Amendment: Safety Report
18-Feb-10	0538	IND Amendment: Safety Report
18-Feb-10	0539	IND Amendment: Safety Report
19-Feb-10	0540	IND Amendment: Safety Report
19-Feb-10	0541	IND Amendment: Safety Report
23-Feb-10	0542	IND Amendment: Safety Report
22-Feb-10	0543	IND Amendment: Safety Report
24-Feb-10	0544	IND Amendment: Safety Report
24-Feb-10	0545	IND Amendment: Safety Report
25-Feb-10	0546	IND Amendment: Safety Report
25-Feb-10	0547	IND Amendment: Safety Report
26-Feb-10	0548	Information Amendment: Pharmacology/Toxicology
26-Feb-10	0549	IND Amendment: Safety Report
1-Mar-10	0550	IND Amendment: Safety Report
1-Mar-10	0551	IND Amendment: Safety Report
2-Mar-10	0552	IND Amendment: Safety Report
2-Mar-10	0553	IND Amendment: Safety Report
3-Mar-10	0554	IND Amendment: Safety Report
3-Mar-10	0555	IND Amendment: Safety Report
4-Mar-10	0556	IND Amendment: Safety Report
4-Mar-10	0557	Protocol Amendment: New Protocol
5-Mar-10	0558	IND Amendment: Safety Report
5-Mar-10	0559	IND Amendment: Safety Report
5-Mar-10	0560	Protocol Amendment: Change in Protocol
9-Mar-10	0561	IND Amendment: Safety Report
11-Mar-10	0562	Information Amendment: Chemistry/Microbiology
16-Mar-10	0563	Protocol Amendment: New Investigator
10-Mar-10	0564	IND Amendment: Safety Report
11-Mar-10	0565	IND Amendment: Safety Report
12-Mar-10	0566	IND Amendment: Safety Report
12-Mar-10	0567	IND Amendment: Safety Report
12-Mar-10	0568	IND Amendment: Safety Report
15-Mar-10	0569	IND Amendment: Safety Report
16-Mar-10	0570	IND Amendment: Safety Report
16-Mar-10	0571	IND Amendment: Safety Report
17-Mar-10	0572	IND Amendment: Safety Report
17-Mar-10	0573	IND Amendment: Safety Report
17-Mar-10	0574	IND Amendment: Safety Report
18-Mar-10	0575	IND Amendment: Safety Report
18-Mar-10	0576	IND Amendment: Safety Report

FDA Submission Date	Serial No.	Type of Submission
19-Mar-10	0577	IND Amendment: Safety Report
19-Mar-10	0578	IND Amendment: Safety Report
23-Mar-10	0579	IND Amendment: Safety Report
19-Mar-10	0580	Other
23-Mar-10	0581	IND Amendment: Safety Report
25-Mar-10	0582	IND Amendment: Safety Report
24-Mar-10	0583	IND Amendment: Safety Report
25-Mar-10	0584	IND Amendment: Safety Report
24-Mar-10	0585	IND Amendment: Safety Report
29-Mar-10	0586	IND Amendment: Safety Report
30-Mar-10	0587	IND Amendment: Safety Report
30-Mar-10	0588	IND Amendment: Safety Report
2-Apr-10	0589	IND Amendment: Safety Report
31-Mar-10	0590	IND Amendment: Safety Report
1-Apr-10	0591	IND Amendment: Safety Report
1-Apr-10	0592	IND Amendment: Safety Report
2-Apr-10	0593	IND Amendment: Safety Report
2-Apr-10	0594	IND Amendment: Safety Report
5-Apr-10	0595	IND Amendment: Safety Report
7-Apr-10	0596	IND Amendment: Safety Report
6-Apr-10	0597	Information Amendment: Pharmacology/Toxicology
8-Apr-10	0598	Protocol Amendment: New Investigator
8-Apr-10	0599	Information Amendment: Pharmacology/Toxicology
7-Apr-10	0600	IND Amendment: Safety Report
9-Apr-10	0601	IND Amendment: Safety Report
9-Apr-10	0602	Protocol Amendment: New Investigator
9-Apr-10	0603	Protocol Amendment: New Investigator
9-Apr-10	0604	Protocol Amendment: New Investigator
9-Apr-10	0605	Protocol Amendment: New Investigator
15-Apr-10	0606	Protocol Amendment: New Investigator
15-Apr-10	0607	Protocol Amendment: New Investigator
9-Apr-10	0608	Information Amendment: Pharmacology/Toxicology
13-Apr-09	0609	Information Amendment: Pharmacology/Toxicology
16-Apr-10	0610	Protocol Amendment: New Investigator
9-Apr-10	0611	Response to FDA request
13-Apr-10	0612	IND Amendment: Safety Report
14-Apr-10	0613	IND Amendment: Safety Report
13-Apr-10	0614	IND Amendment: Safety Report
14-Apr-10	0615	IND Amendment: Safety Report
16-Apr-10	0616	IND Amendment: Safety Report
16-Apr-10	0617	IND Amendment: Safety Report
20-Apr-10	0618	IND Amendment: Safety Report
23-Apr-10	0619	IND Amendment: Safety Report
23-Apr-10	0620	IND Amendment: Safety Report
27-Apr-10	0621	Protocol Amendment: Change in Protocol
26-Apr-10	0622	IND Amendment: Safety Report
28-Apr-10	0623	IND Amendment: Safety Report
29-Apr-10	0624	IND Amendment: Safety Report
28-Apr-10	0625	Protocol Amendment: Change in Protocol
3-May-10	0626	Protocol Amendment: Change in Protocol

FDA Submission Date	Serial No.	Type of Submission
27-Apr-10	0627	Other
4-May-10	0628	IND Amendment: Safety Report
5-May-10	0629	IND Amendment: Safety Report
5-May-10	0630	Protocol Amendment: Change in Protocol
7-May-10	0631	IND Amendment: Safety Report
6-May-10	0632	Information Amendment: Pharmacology/Toxicology
7-May-10	0633	IND Amendment: Safety Report
12-May-10	0634	IND Amendment: Safety Report
12-May-10	0635	IND Amendment: Safety Report
14-May-10	0636	IND Amendment: Safety Report
14-May-10	0637	IND Amendment: Safety Report
20-May-10	0638	IND Amendment: Safety Report
21-May-10	0639	IND Amendment: Safety Report
27-May-10	0640	IND Amendment: Safety Report
27-May-10	0641	IND Amendment: Safety Report
27-May-10	0642	IND Amendment: Safety Report
28-May-10	0643	Annual Report/Other
3-Jun-10	0644	IND Amendment: Safety Report
3-Jun-10	0645	IND Amendment: Safety Report
8-Jun-10	0646	IND Amendment: Safety Report
15-Jun-10	0647	IND Amendment: Safety Report
15-Jun-10	0648	IND Amendment: Safety Report
17-Jun-10	0649	IND Amendment: Safety Report
23-Jun-10	0650	IND Amendment: Safety Report
22-Jun-10	0651	IND Amendment: Safety Report
24-Jun-10	0652	IND Amendment: Safety Report
29-Jun-10	0653	IND Amendment: Safety Report
29-Jun-10	0654	IND Amendment: Safety Report
30-Jun-10	0655	IND Amendment: Safety Report
2-Jul-10	0656	IND Amendment: Safety Report
2-Jul-10	0657	Protocol Amendment: New Investigator
6-Jul-10	0658	IND Amendment: Safety Report
9-Jul-10	0659	IND Amendment: Safety Report
9-Jul-10	0660	IND Amendment: Safety Report
13-Jul-10	0661	IND Amendment: Safety Report
13-Jul-10	0662	General Correspondence
15-Jul-10	0663	IND Amendment: Safety Report
16-Jul-10	0664	IND Amendment: Safety Report
21-Jul-10	0665	IND Amendment: Safety Report
21-Jul-10	0666	IND Amendment: Safety Report
27-Jul-10	0667	IND Amendment: Safety Report
27-Jul-10	0668	IND Amendment: Safety Report
28-Jul-10	0669	IND Amendment: Safety Report
28-Jul-10	0670	IND Amendment: Safety Report
28-Jul-10	0671	IND Amendment: Safety Report
30-Jul-10	0672	General Correspondence
2-Aug-10	0673	IND Amendment: Safety Report
5-Aug-10	0674	IND Amendment: Safety Report
5-Aug-10	0675	IND Amendment: Safety Report
9-Aug-10	0676	IND Amendment: Safety Report

FDA Submission Date	Serial No.	Type of Submission
9-Aug-10	0677	IND Amendment: Safety Report
12-Aug-10	0678	IND Amendment: Safety Report
12-Aug-10	0679	IND Amendment: Safety Report
13-Aug-10	0680	IND Amendment: Safety Report
13-Aug-10	0681	IND Amendment: Safety Report
17-Aug-10	0682	IND Amendment: Safety Report
18-Aug-10	0683	IND Amendment: Safety Report
19-Aug-10	0684	IND Amendment: Safety Report
24-Aug-10	0685	IND Amendment: Safety Report
24-Aug-10	0686	IND Amendment: Safety Report
26-Aug-10	0687	Protocol Amendment: New Investigator
27-Aug-10	0688	Protocol Amendment: New Investigator
27-Aug-10	0689	IND Amendment: Safety Report
30-Aug-10	0690	Protocol Amendment: New Investigator
30-Aug-10	0691	Protocol Amendment: Change in Protocol
30-Aug-10	0692	Protocol Amendment: Change in Protocol
1-Sep-10	0693	IND Amendment: Safety Report
1-Sep-10	0694	IND Amendment: Safety Report
3-Sep-10	0695	Protocol Amendment: New Protocol
3-Sep-10	0696	Other
9-Sep-10	0697	Information Amendment: Pharmacology/Toxicology
8-Sep-10	0698	IND Amendment: Safety Report
8-Sep-10	0699	IND Amendment: Safety Report
14-Sep-10	0700	IND Amendment: Safety Report
10-Sep-10	0701	Response to FDA request
10-Sep-10	0702	Response to FDA request
17-Sep-10	0703	Information Amendment: Chemistry/Microbiology
14-Sep-10	0704	Information Amendment: Clinical
17-Sep-10	0705	IND Amendment: Safety Report
17-Sep-10	0706	IND Amendment: Safety Report
22-Sep-10	0707	Information Amendment: Clinical
20-Sep-10	0708	Information Amendment: Clinical
17-Sep-10	0709	IND Amendment: Safety Report
17-Sep-10	0710	IND Amendment: Safety Report
20-Sep-10	0711	Response to FDA request
21-Sep-10	0712	IND Amendment: Safety Report
21-Sep-10	0713	IND Amendment: Safety Report
21-Sep-10	0714	IND Amendment: Safety Report
21-Sep-10	0715	IND Amendment: Safety Report
22-Sep-10	0716	IND Amendment: Safety Report
22-Sep-10	0717	IND Amendment: Safety Report
23-Sep-10	0718	IND Amendment: Safety Report
23-Sep-10	0719	IND Amendment: Safety Report
23-Sep-10	0720	IND Amendment: Safety Report
28-Sep-10	0721	IND Amendment: Safety Report
28-Sep-10	0722	IND Amendment: Safety Report
11-Oct-11	0723	Other
1-Oct-10	0724	Response to FDA request
29-Sep-10	0725	IND Amendment: Safety Report
29-Sep-10	0726	IND Amendment: Safety Report

FDA Submission Date	Serial No.	Type of Submission
29-Sep-10	0727	IND Amendment: Safety Report
1-Oct-10	0728	IND Amendment: Safety Report
6-Oct-10	0729	General Correspondence
4-Oct-10	0730	IND Amendment: Safety Report
4-Oct-10	0731	IND Amendment: Safety Report
8-Oct-10	0732	IND Amendment: Safety Report
6-Oct-10	0733	IND Amendment: Safety Report
8-Oct-10	0734	IND Amendment: Safety Report
8-Oct-10	0735	IND Amendment: Safety Report
8-Oct-10	0736	IND Amendment: Safety Report
8-Oct-10	0737	IND Amendment: Safety Report
13-Oct-10	0738	IND Amendment: Safety Report
13-Oct-10	0739	IND Amendment: Safety Report
20-Oct-10	0740	General Correspondence
15-Oct-10	0741	Other
15-Oct-10	0742	IND Amendment: Safety Report
15-Oct-10	0743	IND Amendment: Safety Report
18-Oct-10	0744	General Correspondence
20-Oct-10	0745	IND Amendment: Safety Report
20-Oct-10	0746	IND Amendment: Safety Report
20-Oct-10	0747	IND Amendment: Safety Report
22-Oct-10	0748	IND Amendment: Safety Report
22-Oct-10	0749	IND Amendment: Safety Report
22-Oct-10	0750	IND Amendment: Safety Report
25-Oct-10	0751	IND Amendment: Safety Report
26-Oct-10	0752	IND Amendment: Safety Report
26-Oct-10	0753	IND Amendment: Safety Report
26-Oct-10	0754	IND Amendment: Safety Report
26-Oct-10	0755	IND Amendment: Safety Report
28-Oct-10	0756	IND Amendment: Safety Report
28-Oct-10	0757	IND Amendment: Safety Report
29-Oct-10	0758	IND Amendment: Safety Report
3-Nov-10	0759	IND Amendment: Safety Report
3-Nov-10	0760	IND Amendment: Safety Report
5-Nov-10	0761	IND Amendment: Safety Report
5-Nov-10	0762	IND Amendment: Safety Report
5-Nov-10	0763	IND Amendment: Safety Report
8-Nov-10	0764	IND Amendment: Safety Report
9-Nov-10	0765	IND Amendment: Safety Report
9-Nov-10	0766	IND Amendment: Safety Report
12-Nov-10	0767	IND Amendment: Safety Report
12-Nov-10	0768	IND Amendment: Safety Report
12-Nov-10	0769	Information Amendment: Chemistry/Microbiology
12-Nov-10	0770	Response to FDA request
16-Nov-10	0771	IND Amendment: Safety Report
17-Nov-10	0772	IND Amendment: Safety Report
19-Nov-10	0773	IND Amendment: Safety Report
19-Nov-10	0774	General Correspondence
18-Nov-10	0775	IND Amendment: Safety Report
23-Nov-10	0776	IND Amendment: Safety Report

FDA Submission Date	Serial No.	Type of Submission
23-Nov-10	0777	IND Amendment: Safety Report
29-Dec-10	0778	Annual Report
29-Nov-10	0779	IND Amendment: Safety Report
30-Nov-10	0780	IND Amendment: Safety Report
2-Dec-10	0781	IND Amendment: Safety Report
2-Dec-10	0782	IND Amendment: Safety Report
6-Dec-10	0783	IND Amendment: Safety Report
7-Dec-10	0784	Other
13-Dec-10	0785	IND Amendment: Safety Report
16-Dec-10	0786	IND Amendment: Safety Report
20-Dec-10	0787	Protocol Amendment: New Investigator
21-Dec-10	0788	Protocol Amendment: New Investigator
21-Dec-10	0789	General Correspondence
20-Dec-10	0790	Response to FDA request
21-Dec-10	0791	Protocol Amendment: New Protocol
21-Dec-10	0792	IND Amendment: Safety Report
21-Dec-10	0793	IND Amendment: Safety Report
23-Dec-10	0794	Response to FDA request
5-Jan-11	0795	General Correspondence
23-Dec-10	0796	IND Amendment: Safety Report
23-Dec-10	0797	IND Amendment: Safety Report
29-Dec-10	0798	Response to FDA request
27-Dec-10	0799	IND Amendment: Safety Report
27-Dec-10	0800	IND Amendment: Safety Report
30-Dec-10	0801	IND Amendment: Safety Report
3-Jan-11	0802	IND Amendment: Safety Report
3-Jan-11	0803	IND Amendment: Safety Report
7-Jan-11	0804	IND Amendment: Safety Report
7-Jan-11	0805	IND Amendment: Safety Report
10-Jan-11	0806	General Correspondence
10-Jan-11	0807	General Correspondence
10-Jan-11	0808	General Correspondence
18-Jan-11	0809	Protocol Amendment: New Investigator
12-Jan-11	0810	IND Amendment: Safety Report
12-Jan-11	0811	IND Amendment: Safety Report
12-Jan-11	0812	IND Amendment: Safety Report
14-Jan-11	0813	Protocol Amendment: New Investigator
14-Jan-11	0814	IND Amendment: Safety Report
17-Jan-11	0815	IND Amendment: Safety Report
19-Jan-11	0816	IND Amendment: Safety Report
19-Jan-11	0817	IND Amendment: Safety Report
21-Jan-11	0818	IND Amendment: Safety Report
24-Jan-11	0819	Protocol Amendment: New Investigator
26-Jan-11	0820	Information Amendment: Chemistry/Microbiology
25-Jan-11	0821	IND Amendment: Safety Report
25-Jan-11	0822	IND Amendment: Safety Report
28-Jan-11	0823	IND Amendment: Safety Report
1-Feb-11	0824	IND Amendment: Safety Report
2-Feb-11	0825	IND Amendment: Safety Report
1-Feb-11	0826	IND Amendment: Safety Report

FDA Submission Date	Serial No.	Type of Submission
4-Feb-11	0827	Information Amendment: Chemistry/Microbiology
4-Feb-11	0828	IND Amendment: Safety Report
4-Feb-11	0829	IND Amendment: Safety Report
17-Feb-11	0830	Protocol Amendment: Change in Protocol
8-Feb-11	0831	IND Amendment: Safety Report
11-Feb-11	0832	IND Amendment: Safety Report
11-Feb-11	0833	IND Amendment: Safety Report
14-Feb-11	0834	IND Amendment: Safety Report
14-Feb-11	0835	IND Amendment: Safety Report
16-Feb-11	0836	IND Amendment: Safety Report
15-Feb-11	0837	IND Amendment: Safety Report
17-Feb-11	0838	IND Amendment: Safety Report
17-Feb-11	0839	IND Amendment: Safety Report
24-Feb-11	0840	IND Amendment: Safety Report
2-Mar-11	0841	Protocol Amendment: New Investigator
14-Mar-11	0842	Protocol Amendment: New Investigator
15-Mar-11	0843	Protocol Amendment: New Investigator
25-Feb-11	0844	IND Amendment: Safety Report
2-Mar-11	0845	IND Amendment: Safety Report
2-Mar-11	0846	IND Amendment: Safety Report
3-Mar-11	0847	IND Amendment: Safety Report
2-Mar-11	0848	IND Amendment: Safety Report
4-Mar-11	0849	IND Amendment: Safety Report
4-Mar-11	0850	IND Amendment: Safety Report
8-Mar-11	0851	IND Amendment: Safety Report
8-Mar-11	0852	IND Amendment: Safety Report
8-Mar-11	0853	IND Amendment: Safety Report
10-Mar-11	0854	IND Amendment: Safety Report
11-Mar-11	0855	IND Amendment: Safety Report
11-Mar-11	0856	IND Amendment: Safety Report
21-Mar-11	0857	General Correspondence
11-Mar-11	0858	IND Amendment: Safety Report
16-Mar-11	0859	IND Amendment: Safety Report
16-Mar-11	0860	IND Amendment: Safety Report
17-Mar-11	0861	IND Amendment: Safety Report
18-Mar-11	0862	IND Amendment: Safety Report
21-Mar-11	0863	IND Amendment: Safety Report
21-Mar-11	0864	IND Amendment: Safety Report
23-Mar-11	0865	IND Amendment: Safety Report
23-Mar-11	0866	IND Amendment: Safety Report
23-Mar-11	0867	IND Amendment: Safety Report
14-Apr-11	0868	General Correspondence
25-Mar-11	0869	IND Amendment: Safety Report
28-Mar-11	0870	IND Amendment: Safety Report
25-Mar-11	0871	Protocol Amendment: New Investigator
28-Mar-11	0872	Other
28-Mar-11	0873	IND Amendment: Safety Report
28-Mar-11	0874	IND Amendment: Safety Report
29-Mar-11	0875	IND Amendment: Safety Report
31-Mar-11	0876	Response to FDA Request for Information

FDA Submission Date	Serial No.	Type of Submission
31-Mar-11	0877	IND Amendment: Safety Report
31-Mar-11	0878	IND Amendment: Safety Report
1-Apr-11	0879	IND Amendment: Safety Report
4-Apr-11	0880	IND Amendment: Safety Report
5-Apr-11	0881	IND Amendment: Safety Report
5-Apr-11	0882	IND Amendment: Safety Report
6-Apr-11	0883	IND Amendment: Safety Report
8-Apr-11	0884	IND Amendment: Safety Report
11-Apr-11	0885	Response to FDA Request for Information
11-Apr-11	0886	IND Amendment: Safety Report
11-Apr-11	0887	IND Amendment: Safety Report
12-Apr-11	0888	IND Amendment: Safety Report
12-Apr-11	0889	IND Amendment: Safety Report
12-Apr-11	0890	General Correspondence
13-Apr-11	0891	IND Amendment: Safety Report
14-Apr-11	0892	IND Amendment: Safety Report
14-Apr-11	0893	IND Amendment: Safety Report
15-Apr-11	0894	IND Amendment: Safety Report
15-Apr-11	0895	IND Amendment: Safety Report
18-Apr-11	0896	IND Amendment: Safety Report
18-Apr-11	0897	IND Amendment: Safety Report
19-Apr-11	0898	Information Amendment: Pharmacology / Toxicology
20-Apr-11	0899	Protocol Amendment: Change in Protocol and New Investigator
20-Apr-11	0900	IND Amendment: Safety Report
20-Apr-11	0901	IND Amendment: Safety Report
21-Apr-11	0902	IND Amendment: Safety Report
20-Apr-11	0903	Other
21-Apr-11	0904	IND Amendment: Safety Report
21-Apr-11	0905	IND Amendment: Safety Report
25-Apr-11	0906	Protocol Amendment: New Investigator
22-Apr-11	0907	IND Amendment: Safety Report
25-Apr-11	0908	IND Amendment: Safety Report
25-Apr-11	0909	IND Amendment: Safety Report
26-Apr-11	0910	IND Amendment: Safety Report
27-Apr-11	0911	IND Amendment: Safety Report
27-Apr-11	0912	IND Amendment: Safety Report
28-Apr-11	0913	IND Amendment: Safety Report
28-Apr-11	0914	IND Amendment: Safety Report

Table 2. ZYTIGA NDA 202379 SUBMISSION LOG

FDA Submission Date	Serial No.	Type of Submission
17-Dec-2010	0000	Original Application
6-Jan-2011	0001	Amendment to Pending Application
6-Jan-2011	0002	Amendment to Pending Application
27-Jan-2011	0003	Amendment to Pending Application
1-Feb-2011	0004	Amendment to Pending Application

FDA Submission Date	Serial No.	Type of Submission
1-Feb-2011	0005	Amendment to Pending Application
17-Feb-2011	0006	Amendment to Pending Application
22-Feb-2011	0007	Amendment to Pending Application
23-Feb-2011	0008	Amendment to Pending Application
7-Mar-2011	0009	Amendment to Pending Application
14-Mar-2011	0010	Amendment to Pending Application
21-Mar-2011	0011	Amendment to Pending Application
25-Mar-2011	0012	Amendment to Pending Application
28-Mar-2011	0013	Amendment to Pending Application
30-Mar-2011	0014	Amendment to Pending Application
31-Mar-2011	0015	Amendment to Pending Application
4-Apr-2011	0016	Amendment to Pending Application
12-Apr-2011	0017	Amendment to Pending Application
8-Apr-2011	0018	Amendment to Pending Application
13-Apr-2011	0019	Amendment to Pending Application
18-Apr-2011	0020	Amendment to Pending Application
19-Apr-2011	0021	Amendment to Pending Application
22-Apr-2011	0022	Amendment to Pending Application
22-Apr-2011	0023	Amendment to Pending Application
26-Apr-2011	0024	Amendment to Pending Application
28-Apr-2011	0025	Amendment to Pending Application

J. STATEMENT THAT APPLICANT IS ELIGIBLE FOR EXTENSION (1.740(a)(12))

In the opinion of the Applicant, the '213 Patent is eligible for extension. In the opinion of the applicant, the '213 Patent is entitled to an extension of 1024 days, setting the patent to expire on December 8, 2016.

The following are the calculations, made in accordance with 37 C.F.R. § 1.775, that result in the claimed extension:

(1) The testing phase began on January 28, 2006 (the effective date of the IND) and ended on December 20, 2010 (day of receipt by the FDA of the NDA).

(2) The approval phase began on December 20, 2010 (day of receipt by the FDA of the NDA) and ended on April 28, 2011, when approval was granted.

(3) The total number of days in the testing phase (from and including January 28, 2006 to December 20, 2010) is 1788 days from the start date to the end date, end date included. One half of the testing phase is 894 days.

(4) The total number of days in the approval phase is (from and including December 20, 2010 to and including April 28, 2011) is 130 days from the start date to the end date, end date included.

(5) The patent issued on February 18, 1997 before the regulatory approval process began.

(6) Applicant acted with due diligence throughout the entire regulatory review period.

(7) The sum of the (a) number of days in one half of the testing phase (894), and (b) number of days in the approval phase (130) is: 1024.

(8) The original expiration date of the patent is February 18, 2014.

(9) Addition of the extension of 1024 days to the original expiration date of the patent extends the expiration date of the patent to December 8, 2016.

(10) Fourteen years from the approval date of the product (April 28, 2011) is April 28, 2025.

(11) Pursuant to 35 U.S.C. §156(c)(3), the extended term of the patent cannot exceed 14 years from the date of product approval. The fourteen year cap does not apply since the extension of 1024 days sets the patent to expire on December 8, 2016, which is before the date that is 14 years post-approval (April 28, 2025).

(12) Pursuant to 35 U.S.C. §156(g)(6)(A), the extension period is subject to a five year limitation (for patents issued after September 24, 1984). The five year limitation does not apply since the extension of 1024 days patent is less than five years.

(13) In light of the conclusions set forth above, the extended expiration date of the

'213 Patent is believed to be December 8, 2016.

K. ACKNOWLEDGEMENT OF DUTY OF DISCLOSURE (1.740(a)(13))

I, Leonard C. Mitchard, the person signing below, acknowledge the duty to disclose to the Director of the U.S. Patent and Trademark Office and to the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension which is being sought herein.

L. FEE (1.740(a)(14))

The requisite fee of $1120.00 (37 C.F.R. §1.20(j)) is submitted herewith. The Commissioner is authorized to charge any deficiency in the fee submitted, or credit any overpayment, to Deposit Account No. 14-1140 under docket number 604-848.

M. CORRESPONDENCE

Please direct all inquiries and correspondence relating to this application to:

Leonard C. Mitchard, Esq.
NIXON & VANDERHYE P.C.
901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100

N. COPIES (§ MPEP 2753 (8th Edition, Rev. No. 4))

Four additional copies of this application are attached, making a total of five copies being submitted.

O. POWER OF ATTORNEY (1.730(a)(2) and (d))

The undersigned is authorized to act on behalf of the Applicant by virtue of the signed Power of Attorney submitted herewith as Exhibit 1.

Conclusion

In conclusion, on the basis of the information provided herein, Applicant respectfully asserts that U.S. Patent No. 5,604,213 is entitled to the requested 1024 day extension of its term to December 8, 2016.

Prompt action on this application is respectfully requested.

/Leonard C. Mitchard/
Leonard C. Mitchard, 29,009

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	PTO Conf. No.: 4753
BARRIE et al	Atty. Ref.: 604-848
Patent No. 5,604,213	Group: 1202
Filed: February 18, 1997	Examiner: Bottino, A.

For: 17-SUBSTITUTED STEROIDS USEFUL IN CANCER TREATMENT

* * * * * * * * * * *

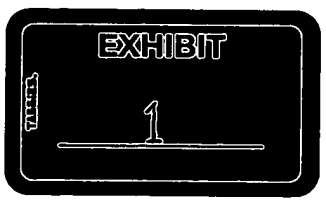
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

EXCLUSIVE SUBSTITUTE POWER OF ATTORNEY AND EXCLUSIVE PROSECUTION HEREAFTER BY ASSIGNEE UNDER 37 C.F.R. §§ 1.36, 3.71 AND 3.73

BTG International Ltd., being the owner of all right, title and interest in the above-identified patent application, hereby revokes all previous powers of attorney in this case, if any, and hereby appoints the attorneys of **Customer Number 23117** individually and collectively its attorneys to prosecute this application and to transact all business in the Patent and Trademark Office in connection therewith, and with the resulting patent.

BTG International Ltd. also authorizes Nixon & Vanderhye P.C. to act and rely solely on instructions communicated from the person, attorney, firm or other organization sending instructions to Nixon & Vanderhye P.C. on behalf of the owner.



BARRIE et al
Serial No. 5,604,213

Certificate Under 37 C.F.R. §3.73(b)

BTG International Ltd., a corporation having a place of business at 5, Fleet Place, London England EC4M 7RD states that it is the assignee of the entire right, title and interest in the patent application identified above by virtue of an assignment from the inventors to the aforesaid assignee, a copy of the assignment being recorded at the United States Patent Office on September 30, 1994 at reel 007172, frame 0859 and a change of name recorded at the United States Patent Office on November 15, 2010, at Reel 025364, Frame 0584.

The undersigned (whose title is typed below) is empowered to sign this statement on behalf of BTG International Ltd..

BTG International Ltd.

20 June 2011 By: _____
Date

Name: Louise Makin
Title: Chief Executive Officer

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZYTIGA safely and effectively. See full prescribing information for ZYTIGA.

ZYTIGA™ (abiraterone acetate) Tablets
For Oral Administration
Initial U.S. Approval – 2011

----------INDICATIONS AND USAGE----------

ZYTIGA is a CYP17 inhibitor indicated for use in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel. (1)

----------DOSAGE AND ADMINISTRATION----------

Recommended dose: ZYTIGA 1,000 mg administered orally once daily in combination with prednisone 5 mg administered orally twice daily. ZYTIGA must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken. (2.1)

- For patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the ZYTIGA starting dose to 250 mg once daily. (2.2)
- For patients who develop hepatotoxicity during treatment, hold ZYTIGA until recovery. Retreatment may be initiated at a reduced dose. ZYTIGA should be discontinued if patients develop severe hepatotoxicity. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Tablet 250 mg (3)

----------CONTRAINDICATIONS----------

- ZYTIGA is contraindicated in women who are or may become pregnant. (4.1)

----------WARNINGS AND PRECAUTIONS----------

- Mineralocorticoid excess: Use ZYTIGA with caution in patients with a history of cardiovascular disease. The safety of ZYTIGA in patients with LVEF < 50% or NYHA Class III or IV heart failure is not established. Control hypertension and correct hypokalemia before treatment. Monitor blood pressure, serum potassium and symptoms of fluid retention at least monthly. (5.1)
- Adrenocortical insufficiency: Monitor for symptoms and signs of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations. (5.2)
- Hepatotoxicity: Increases in liver enzymes have lead to drug interruption, dose modification and/or discontinuation. Monitor liver function and modify, interrupt, or discontinue ZYTIGA dosing as recommended. (5.3)
- Food Effect: ZYTIGA must be taken on an empty stomach. Exposure (area under the curve) of abiraterone increases up to 10 fold when abiraterone acetate is taken with meals. (5.4)

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥ 5%) are joint swelling or discomfort, hypokalemia, edema, muscle discomfort, hot flush, diarrhea, urinary tract infection, cough, hypertension, arrhythmia, urinary frequency, nocturia, dyspepsia, and upper respiratory tract infection. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Centocor Ortho Biotech Inc. at 800-457-6399 and *www.centocororthobiotech.com* or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

ZYTIGA is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. Avoid co-administration of ZYTIGA with CYP2D6 substrates that have a narrow therapeutic index. If an alternative treatment cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate. (7)

----------USE IN SPECIFIC POPULATIONS----------

- Do not use ZYTIGA in patients with baseline severe hepatic impairment (Child-Pugh Class C). (8.6)

See 17 for Patient Counseling Information and FDA-approved patient labeling.

Issued: [April 2011]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

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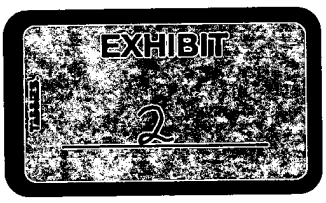


FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZYTIGA in combination with prednisone is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC) who have received prior chemotherapy containing docetaxel.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of ZYTIGA is 1,000 mg administered orally once daily in combination with prednisone 5 mg administered orally twice daily. ZYTIGA must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken *[see Clinical Pharmacology (12.3)]*. The tablets should be swallowed whole with water.

2.2 Dose Modification Guidelines

Hepatic Impairment

In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of ZYTIGA to 250 mg once daily. A once daily dose of 250 mg in patients with moderate hepatic impairment is predicted to result in an area under the concentration curve (AUC) similar to the AUC seen in patients with normal hepatic function receiving 1,000 mg once daily. However, there are no clinical data at the dose of 250 mg once daily in patients with moderate hepatic impairment and caution is advised. In patients with moderate hepatic impairment monitor ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. If elevations in ALT and/or AST greater than 5X upper limit of normal (ULN) or total bilirubin greater than 3X ULN occur in patients with baseline moderate hepatic impairment, discontinue ZYTIGA and do not re-treat patients with ZYTIGA *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

Avoid ZYTIGA in patients with baseline severe hepatic impairment (Child-Pugh Class C), as ZYTIGA has not been studied in this population, and no dose adjustment can be predicted.

Hepatotoxicity

For patients who develop hepatotoxicity during treatment with ZYTIGA (ALT and/or AST greater than 5X ULN or total bilirubin greater than 3X ULN), interrupt treatment with ZYTIGA *[see Warnings and Precautions (5.3)]*. Treatment may be restarted at a reduced dose of 750 mg once daily following return of liver function tests to the patient's baseline or

to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN. For patients who resume treatment, monitor serum transaminases and bilirubin at a minimum of every two weeks for three months and monthly thereafter.

If hepatotoxicity recurs at the dose of 750 mg once daily, re-treatment may be restarted at a reduced dose of 500 mg once daily following return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN.

If hepatotoxicity recurs at the reduced dose of 500 mg once daily, discontinue treatment with ZYTIGA. The safety of ZYTIGA re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

3 DOSAGE FORMS AND STRENGTHS

ZYTIGA (abiraterone acetate) 250 mg tablets are white to off-white, oval-shaped tablets debossed with AA250 on one side.

4 CONTRAINDICATIONS

4.1 Pregnancy

ZYTIGA may cause fetal harm when administered to a pregnant woman. ZYTIGA is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

5 WARNINGS AND PRECAUTIONS

5.1 Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess

Use ZYTIGA with caution in patients with a history of cardiovascular disease. ZYTIGA may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition *[see Adverse Reactions (6) and Clinical Pharmacology (12.1)]*. Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in the incidence and severity of these adverse reactions. Use caution when treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, e.g., those with heart failure, recent myocardial infarction or ventricular arrhythmia. The safety of ZYTIGA in patients with left ventricular ejection fraction <50% or NYHA Class III or IV heart failure has not been established because these patients were excluded from the randomized clinical trial. Monitor patients for hypertension, hypokalemia,

and fluid retention at least once a month. Control hypertension and correct hypokalemia before and during treatment with ZYTIGA.

5.2 Adrenocortical Insufficiency

Adrenocortical insufficiency has been reported in clinical trials in patients receiving ZYTIGA in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress. Use caution and monitor for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with ZYTIGA. If clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations *[see Warnings and Precautions (5.1)]*.

5.3 Hepatotoxicity

Marked increases in liver enzymes leading to drug discontinuation or dosage modification have occurred *[see Adverse Reactions (6)]*. Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with ZYTIGA, every two weeks for the first three months of treatment and monthly thereafter. In patients with baseline moderate hepatic impairment receiving a reduced ZYTIGA dose of 250 mg, measure ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient's baseline should prompt more frequent monitoring. If at any time AST or ALT rise above five times the ULN, or the bilirubin rises above three times the ULN, interrupt ZYTIGA treatment and closely monitor liver function.

Re-treatment with ZYTIGA at a reduced dose level may take place only after return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN *[see Dosage and Administration (2.2)]*.

The safety of ZYTIGA re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

5.4 Food effect

ZYTIGA must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of

ZYTIGA is taken. Abiraterone C_{max} and $AUC_{0-\infty}$ (exposure) were increased up to 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was administered with a meal compared to a fasted state. The safety of these increased exposures when multiple doses of abiraterone acetate are taken with food has not been assessed *[see Dosage and Administration (2.1) and Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Hypertension, hypokalemia, and fluid retention due to mineralocorticoid excess *[see Warnings and Precautions (5.1)]*.
- Adrenocortical insufficiency *[see Warnings and Precautions (5.2)]*.
- Hepatotoxicity *[see Warnings and Precautions (5.3)]*.
- Food effect *[see Warnings and Precautions (5.4)]*.

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In a placebo-controlled, multicenter phase 3 clinical trial of patients with metastatic castration-resistant prostate cancer who were using a gonadotropin-releasing hormone (GnRH) agonist or were previously treated with orchiectomy, ZYTIGA was administered at a dose of 1,000 mg daily in combination with prednisone 5 mg twice daily in the active treatment arm (N = 791). Placebo plus prednisone 5 mg twice daily was given to control patients (N = 394). The median duration of treatment with ZYTIGA was 8 months.

The most common adverse drug reactions (≥5%) reported in clinical studies were joint swelling or discomfort, hypokalemia, edema, muscle discomfort, hot flush, diarrhea, urinary tract infection, cough, hypertension, arrhythmia, urinary frequency, nocturia, dyspepsia, and upper respiratory tract infection.

The most common adverse drug reactions that resulted in drug discontinuation were aspartate aminotransferase increased, alanine aminotransferase increased, urosepsis and cardiac failure (each in <1% of patients taking ZYTIGA).

Adverse reactions and laboratory abnormalities related to mineralocorticoid effects were reported more commonly in patients treated with ZYTIGA than in patients treated with placebo: hypokalemia 28% versus 20%, hypertension 9% versus 7% and fluid retention (edema) 27% versus 18%, respectively (see Table 1). In patients treated with ZYTIGA,

grades 3 to 4 hypokalemia occurred in 5% of patients and grades 3 to 4 hypertension was reported in 1% of patients *[see Warnings and Precautions (5.1)]*.

Table 1 shows adverse reactions due to ZYTIGA that occurred with either a ≥ 2% absolute increase in frequency compared to placebo, or were events of special interest (mineralocorticoid excess, cardiac adverse reactions, and liver toxicities).

Table 1: Adverse Reactions due to ZYTIGA in a Placebo-Controlled Phase 3 Trial

	ZYTIGA with Prednisone (N=791)		Placebo with Prednisone (N=394)	
System/Organ Class	All Grades[1]	Grade 3-4	All Grades	Grade 3-4
Adverse reaction	%	%	%	%
Musculoskeletal and connective tissue disorders				
Joint swelling/ discomfort[2]	29.5	4.2	23.4	4.1
Muscle discomfort[3]	26.2	3.0	23.1	2.3
General disorders				
Edema[4]	26.7	1.9	18.3	0.8
Vascular disorders				
Hot flush	19.0	0.3	16.8	0.3
Hypertension	8.5	1.3	6.9	0.3
Gastrointestinal disorders				
Diarrhea	17.6	0.6	13.5	1.3
Dyspepsia	6.1	0	3.3	0
Infections and infestations				
Urinary tract infection	11.5	2.1	7.1	0.5
Upper respiratory tract infection	5.4	0	2.5	0
Respiratory, thoracic and mediastinal disorders				
Cough	10.6	0	7.6	0
Renal and urinary disorders				
Urinary frequency	7.2	0.3	5.1	0.3
Nocturia	6.2	0	4.1	0
Cardiac disorders				
Arrhythmia[5]	7.2	1.1	4.6	1.0
Chest pain or chest discomfort[6]	3.8	0.5	2.8	0
Cardiac failure[7]	2.3	1.9	1.0	0.3

[1] Adverse events graded according to CTCAE version 3.0
[2] Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness,
[3] Includes terms Muscle spasms, Musculoskeletal pain, Myalgia, Musculoskeletal discomfort, and Musculoskeletal stiffness
[4] Includes terms Edema, Edema peripheral, Pitting edema, and Generalised edema
[5] Includes terms Arrhythmia, Tachycardia, Atrial fibrillation, Supraventricular tachycardia, Atrial tachycardia, Ventricular tachycardia, Atrial flutter, Bradycardia, Atrioventricular block complete, Conduction disorder, and Bradyarrhythmia.
[6] Includes terms Angina pectoris, Chest pain, and Angina unstable. Myocardial infarction or ischemia occurred more commonly in the placebo arm than in the ZYTIGA arm (1.3% vs. 1.1% respectively).
[7] Includes terms Cardiac failure, Cardiac failure congestive, Left ventricular dysfunction, Cardiogenic shock, Cardiomegaly, Cardiomyopathy, and Ejection fraction decreased

Cardiovascular Adverse Reactions:

Cardiovascular adverse reactions in the phase 3 trial are shown in Table 1. The majority of arrhythmias were grade 1 or 2. Grade 3-4 arrhythmias occurred at similar rates in the two arms. There was one death associated with arrhythmia and one patient with sudden death in the ZYTIGA arm. No patients had sudden death or arrhythmia associated with death in the placebo arm. Cardiac ischemia or myocardial infarction led to death in 2 patients in the placebo arm and 1 death in the ZYTIGA arm. Cardiac failure resulting in death occurred in 1 patient on both arms.

Hepatotoxicity:
Drug-associated hepatotoxicity with elevated ALT, AST, and total bilirubin has been reported in patients treated with ZYTIGA. Across all clinical trials, liver function test elevations (ALT or AST increases of > 5X ULN) were reported in 2.3% of patients who received ZYTIGA, typically during the first 3 months after starting treatment. In the phase 3 trial, patients whose baseline ALT or AST were elevated were more likely to experience liver function test elevations than those beginning with normal values. When elevations of either ALT or AST > 5X ULN, or elevations in bilirubin > 3X ULN were observed, ZYTIGA was withheld or discontinued. In two instances marked increases in liver function tests occurred *[see Warnings and Precautions (5.2)]*. These two patients with normal baseline hepatic function, experienced ALT or AST elevations 15 to 40X ULN and bilirubin elevations 2 to 6 X ULN. Upon discontinuation of ZYTIGA, both patients had normalization of their liver function tests and one patient was re-treated with ZYTIGA without recurrence of the elevations.

In clinical trials, the following patients were excluded: patients with active hepatitis, patients with baseline ALT and/or AST ≥ 2.5X ULN in the absence of liver metastases, and patients with ALT and/or AST > 5X ULN in the presence of liver metastases. Abnormal liver function tests developing in patients participating in clinical trials were managed by treatment interruption, dose modification and/or discontinuation *[see Dosage and Administration (2.2) and Warnings and Precautions (5.3)]*. Patients with elevations of ALT or AST > 20X ULN were not re-treated.

Other Adverse Reactions:
Adrenal insufficiency occurred in two patients on the abiraterone arm of the phase 3 clinical trial (< 1%).

Laboratory Abnormalities of Interest:

Table 2 shows laboratory values of interest from the phase 3 placebo-controlled clinical trial. Grade 3-4 low serum phosphate (7.2%) and potassium (5.3%) occurred more frequently in the ZYTIGA arm.

Table 2: Laboratory Abnormalities of Interest in a Phase 3 Placebo-Controlled Clinical Trial

Laboratory Abnormality	Abiraterone (N=791)		Placebo (N=394)	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
High Triglyceride	62.5	0.4	53.0	0
High AST	30.6	2.1	36.3	1.5
Low Potassium	28.3	5.3	19.8	1.0
Low Phosphorus	23.8	7.2	15.7	5.8
High ALT	11.1	1.4	10.4	0.8
High total Bilirubin	6.6	0.1	4.6	0

7 DRUG INTERACTIONS

7.1 Effects of Abiraterone on Drug Metabolizing Enzymes

ZYTIGA is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. In a CYP2D6 drug-drug interaction trial, the C_{max} and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1,000 mg daily and prednisone 5 mg twice daily. Avoid co-administration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug *[see Clinical Pharmacology (12.3)]*.

7.2 Drugs that Inhibit or Induce CYP3A4 Enzymes

Based on *in vitro* data, ZYTIGA is a substrate of CYP3A4. The effects of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) or inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) on the pharmacokinetics of abiraterone have not been evaluated, *in vivo*. Avoid or use with caution, strong inhibitors and inducers of CYP3A4 during ZYTIGA treatment *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X *[see Contraindications (4.1)]*.

ZYTIGA is contraindicated in women who are or may become pregnant while receiving the drug. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus and the potential risk for pregnancy loss. Women of childbearing potential should be advised to avoid becoming pregnant during treatment with ZYTIGA.

8.3 Nursing Mothers

ZYTIGA is not indicated for use in women. It is not known if abiraterone acetate is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ZYTIGA, a decision should be made to either discontinue nursing, or discontinue the drug taking into account the importance of the drug to the mother.

8.4 Pediatric Use

ZYTIGA is not indicated in children.

8.5 Geriatric Use

Of the total number of patients in a phase 3 trial of ZYTIGA, 71% of patients were 65 years and over and 28% were 75 years and over. No overall differences in safety or effectiveness were observed between these elderly patients and younger patients.

8.6 Patients with Hepatic Impairment

The pharmacokinetics of abiraterone were examined in subjects with baseline mild (n = 8) or moderate (n = 8) hepatic impairment (Child-Pugh Class A and B, respectively) and in 8 healthy control subjects with normal hepatic function. The systemic exposure (AUC) of abiraterone after a single oral 1,000 mg dose of ZYTIGA increased by approximately 1.1-fold and 3.6 fold in subjects with mild and moderate baseline hepatic impairment, respectively compared to subjects with normal hepatic function.

No dosage adjustment is necessary for patients with baseline mild hepatic impairment. In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of ZYTIGA to 250 mg once daily. If elevations in ALT or AST >5X ULN or total bilirubin >3X ULN occur in patients with baseline moderate hepatic impairment, discontinue ZYTIGA treatment *[see Dosage and Administration (2.1) and Clinical Pharmacology (12.3)]*.

The safety of ZYTIGA in patients with baseline severe hepatic impairment has not been studied. These patients should not receive ZYTIGA.

For patients who develop hepatotoxicity during treatment, interruption of treatment and dosage adjustment may be required *[see Dosage and Administration (2.2), Warnings and Precautions (5.2), and Clinical Pharmacology (12.3)]*.

8.7 Patients with Renal Impairment

In a dedicated renal impairment trial, the mean PK parameters were comparable between healthy subjects with normal renal function (N=8) and those with end stage renal disease (ESRD) on hemodialysis (N=8) after a single oral 1,000 mg dose of ZYTIGA. No dosage adjustment is necessary for patients with renal impairment *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

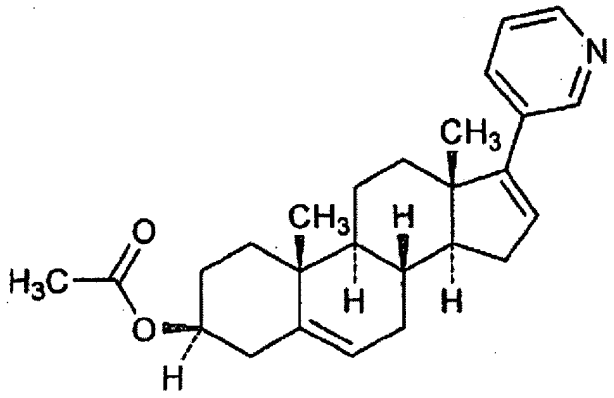
10 OVERDOSAGE

There have been no reports of overdose of ZYTIGA during clinical studies.

There is no specific antidote. In the event of an overdose, stop ZYTIGA, undertake general supportive measures, including monitoring for arrhythmias and cardiac failure and assess liver function.

11 DESCRIPTION

Abiraterone acetate, the active ingredient of ZYTIGA is the acetyl ester of abiraterone. Abiraterone is an inhibitor of CYP17 (17α-hydroxylase/C17,20-lyase). Each ZYTIGA tablet contains 250 mg of abiraterone acetate. Abiraterone acetate is designated chemically as (3β)-17-(3-pyridinyl)androsta-5,16-dien-3-yl acetate and its structure is:



Abiraterone acetate is a white to off-white, non-hygroscopic, crystalline powder. Its molecular formula is $C_{26}H_{33}NO_2$ and it has a molecular weight of 391.55. Abiraterone acetate is a lipophilic compound with an octanol-water partition coefficient of 5.12 (Log P) and is practically insoluble in water. The pKa of the aromatic nitrogen is 5.19.

Inactive ingredients in the tablets are lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulfate, magnesium stearate, and colloidal silicon dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Abiraterone acetate (ZYTIGA) is converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor, that inhibits 17 α-hydroxylase/C17,20-lyase (CYP17). This enzyme is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis.

CYP17 catalyzes two sequential reactions: 1) the conversion of pregnenolone and progesterone to their 17α-hydroxy derivatives by 17α-hydroxylase activity and 2) the subsequent formation of dehydroepiandrosterone (DHEA) and androstenedione, respectively, by C17, 20 lyase activity. DHEA and androstenedione are androgens and are precursors of testosterone. Inhibition of CYP17 by abiraterone can also result in increased mineralocorticoid production by the adrenals *(see Warnings and Precautions [5.1])*.

Androgen sensitive prostatic carcinoma responds to treatment that decreases androgen levels. Androgen deprivation therapies, such as treatment with GnRH agonists or orchiectomy, decrease androgen production in the testes but do not affect androgen production by the adrenals or in the tumor.

ZYTIGA decreased serum testosterone and other androgens in patients in the placebo-controlled phase 3 clinical trial. It is not necessary to monitor the effect of ZYTIGA on serum testosterone levels.

Changes in serum prostate specific antigen (PSA) levels may be observed but have not been shown to correlate with clinical benefit in individual patients.

12.3 Pharmacokinetics

Following administration of abiraterone acetate, the pharmacokinetics of abiraterone and abiraterone acetate have been studied in healthy subjects and in patients with metastatic castration-resistant prostate cancer (CRPC). *In vivo*, abiraterone acetate is converted to abiraterone. In clinical studies, abiraterone acetate plasma concentrations were below detectable levels (< 0.2 ng/mL) in > 99% of the analyzed samples.

Absorption

Following oral administration of abiraterone acetate to patients with metastatic CRPC, the median time to reach maximum plasma abiraterone concentrations is 2 hours. Abiraterone

accumulation is observed at steady-state, with a 2-fold higher exposure (steady-state AUC) compared to a single 1,000 mg dose of abiraterone acetate.

At the dose of 1,000 mg daily in patients with metastatic CRPC, steady-state values (mean ± SD) of C_{max} were 226 ± 178 ng/mL and of AUC were 1173 ± 690 ng.hr/mL. No major deviation from dose proportionality was observed in the dose range of 250 mg to 1,000 mg.

Systemic exposure of abiraterone is increased when abiraterone acetate is administered with food. Abiraterone C_{max} and $AUC_{0-\infty}$ were approximately 7- and 5-fold higher, respectively, when abiraterone acetate was administered with a low-fat meal (7% fat, 300 calories) and approximately 17- and 10-fold higher, respectively, when abiraterone acetate was administered with a high-fat (57% fat, 825 calories) meal. Given the normal variation in the content and composition of meals, taking ZYTIGA with meals has the potential to result in increased and highly variable exposures. Therefore, no food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken. The tablets should be swallowed whole with water *[see Dosage and Administration (2.1)]*.

Distribution and Protein Binding

Abiraterone is highly bound (>99%) to the human plasma proteins, albumin and alpha-1 acid glycoprotein. The apparent steady-state volume of distribution (mean ± SD) is 19,669 ± 13,358 L. *In vitro* studies show that at clinically relevant concentrations, abiraterone acetate and abiraterone are not substrates of P-glycoprotein (P-gp) and that abiraterone acetate is an inhibitor of P-gp. No studies have been conducted with other transporter proteins.

Metabolism

Following oral administration of ^{14}C-abiraterone acetate as capsules, abiraterone acetate is hydrolyzed to abiraterone (active metabolite). The conversion is likely through esterase activity (the esterases have not been identified) and is not CYP mediated. The two main circulating metabolites of abiraterone in human plasma are abiraterone sulphate (inactive) and N-oxide abiraterone sulphate (inactive), which account for about 43% of exposure each. CYP3A4 and SULT2A1 are the enzymes involved in the formation of N-oxide abiraterone sulphate and SULT2A1 is involved in the formation of abiraterone sulphate.

Excretion

In patients with metastatic CRPC, the mean terminal half-life of abiraterone in plasma (mean ± SD) is 12 ± 5 hours. Following oral administration of ^{14}C-abiraterone acetate, approximately 88% of the radioactive dose is recovered in feces and approximately 5% in

urine. The major compounds present in feces are unchanged abiraterone acetate and abiraterone (approximately 55% and 22% of the administered dose, respectively).

Patients with Hepatic Impairment

The pharmacokinetics of abiraterone was examined in subjects with baseline mild (n = 8) or moderate (n = 8) hepatic impairment (Child-Pugh Class A and B, respectively) and in 8 healthy control subjects with normal hepatic function. Systemic exposure to abiraterone after a single oral 1,000 mg dose given under fasting conditions increased approximately 1.1-fold and 3.6-fold in subjects with mild and moderate baseline hepatic impairment, respectively. The mean half-life of abiraterone is prolonged to approximately 18 hours in subjects with mild hepatic impairment and to approximately 19 hours in subjects with moderate hepatic impairment. ZYTIGA has not been studied in patients with baseline severe hepatic impairment (Child-Pugh Class C) *[see Dosage and Administration (2.2) and Use in Specific Populations (8.6)]*.

Patients with Renal Impairment

The pharmacokinetics of abiraterone were examined in patients with end-stage renal disease (ESRD) on a stable hemodialysis schedule (N=8) and in matched control subjects with normal renal function (N=8). In the ESRD cohort of the trial, a single 1,000 mg ZYTIGA dose was given under fasting conditions 1 hour after dialysis, and samples for pharmacokinetic analysis were collected up to 96 hours post dose. Systemic exposure to abiraterone after a single oral 1,000 mg dose did not increase in subjects with end-stage renal disease on dialysis, compared to subjects with normal renal function *[see Use in Specific Populations (8.7)]*.

Drug Interactions

In vitro studies with human hepatic microsomes showed that abiraterone is a strong inhibitor of CYP1A2 and CYP2D6 and a moderate inhibitor of CYP2C9, CYP2C19 and CYP3A4/5.

In an *in vivo* drug-drug interaction trial, the C_{max} and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively when dextromethorphan 30 mg was given with abiraterone acetate 1,000 mg daily (plus prednisone 5 mg twice daily). The AUC for dextrorphan, the active metabolite of dextromethorphan, increased approximately 1.3 fold *[see Drug Interactions (7.1)]*.

In a clinical study to determine the effects of abiraterone acetate 1,000 mg daily (plus prednisone 5 mg twice daily) on a single 100 mg dose of the CYP1A2 substrate theophylline, no increase in systemic exposure of theophylline was observed.

Abiraterone is a substrate of CYP3A4, *in vitro*. The effects of strong CYP3A4 inhibitors or inducers on the pharmacokinetics of abiraterone have not been evaluated, *in vivo*. Strong inhibitors and inducers of CYP3A4 should be avoided or used with caution *[see Drug Interactions (7.2)]*.

12.4 QT Prolongation

In a multi-center, open-label, single-arm trial, 33 patients with metastatic CRPC received ZYTIGA orally at a dose of 1,000 mg once daily at least 1 hour before or 2 hours after a meal in combination with prednisone 5 mg orally twice daily. Assessments up to Cycle 2 Day 2 showed no large changes in the QTc interval (i.e., >20 ms) from baseline. However, small increases in the QTc interval (i.e., <10 ms) due to abiraterone acetate cannot be excluded due to study design limitations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of abiraterone acetate.

Abiraterone acetate and abiraterone did not induce mutations in the microbial mutagenesis (Ames) assay and was not clastogenic in both the *in vitro* cytogenetic assay using primary human lymphocytes and in the *in vivo* rat micronucleus assay.

Developmental or reproductive toxicology studies were not conducted with abiraterone acetate. In studies in rats (13- and 26-weeks) and monkeys (39-weeks), atrophy, aspermia/hypospermia, and hyperplasia in the reproductive system were observed at ≥50 mg/kg/day in rats and ≥250 mg/kg/day in monkeys and were consistent with the antiandrogenic pharmacological activity of abiraterone *[see Nonclinical Toxicology (13.2.)]*. These effects were observed in rats and monkeys at approximately 1.14 and 0.6 the human clinical exposure based on AUC, respectively.

13.2 Animal Toxicology and/or Pharmacology

In 13- and 26-week studies in rats and 13- and 39-week studies in monkeys, a reduction in circulating testosterone levels occurred with abiraterone acetate at approximately one half the human clinical exposure based on AUC. As a result, decreases in organ weights and toxicities were observed in the male and female reproductive system, adrenal glands, liver, pituitary (rats only), and male mammary glands. The changes in the reproductive organs are consistent with the antiandrogenic pharmacological activity of abiraterone acetate. A dose-dependent increase in cataracts was observed in rats at 26 weeks starting at ≥50 mg/kg/day (1.14X the human clinical exposure based on AUC). In the 39-week monkey study, no

cataracts were observed at higher doses (2X the clinical exposure based on AUC). All other toxicities associated with abiraterone acetate reversed or were partially resolved after a 4-week recovery period.

14 CLINICAL STUDIES

The efficacy and safety of ZYTIGA in patients with metastatic castration-resistant prostate cancer (CRPC) who had received prior chemotherapy containing docetaxel were assessed in a randomized, placebo-controlled, multicenter phase 3 clinical trial. A total of 1195 patients were randomized 2:1 to receive either ZYTIGA orally at a dose of 1,000 mg once daily in combination with prednisone 5 mg orally twice daily (N=797) or placebo once daily plus prednisone 5 mg orally twice daily (N=398). Patients randomized to either arm were to continue treatment until disease progression (defined as a 25% increase in PSA over the patient's baseline/nadir together with protocol-defined radiographic progression and symptomatic or clinical progression), initiation of new treatment, unacceptable toxicity or withdrawal. Patients with prior ketoconazole treatment for prostate cancer and a history of adrenal gland or pituitary disorders were excluded from this trial.

The following patient demographics and baseline disease characteristics were balanced between the treatment arms. The median age was 69 years (range 39-95) and the racial distribution was 93.3% Caucasian, 3.6% Black, 1.7% Asian, and 1.6% Other. Eighty-nine percent of patients enrolled had an ECOG performance status score of 0-1 and 45% had a Brief Pain Inventory score of $\geq$ 4 (patient's reported worst pain over the previous 24 hours). Ninety percent of patients had metastases in bone and 30% had visceral involvement. Seventy percent of patients had radiographic evidence of disease progression and 30% had PSA-only progression. Seventy percent of patients had previously received one cytotoxic chemotherapy regimen and 30% received two regimens.

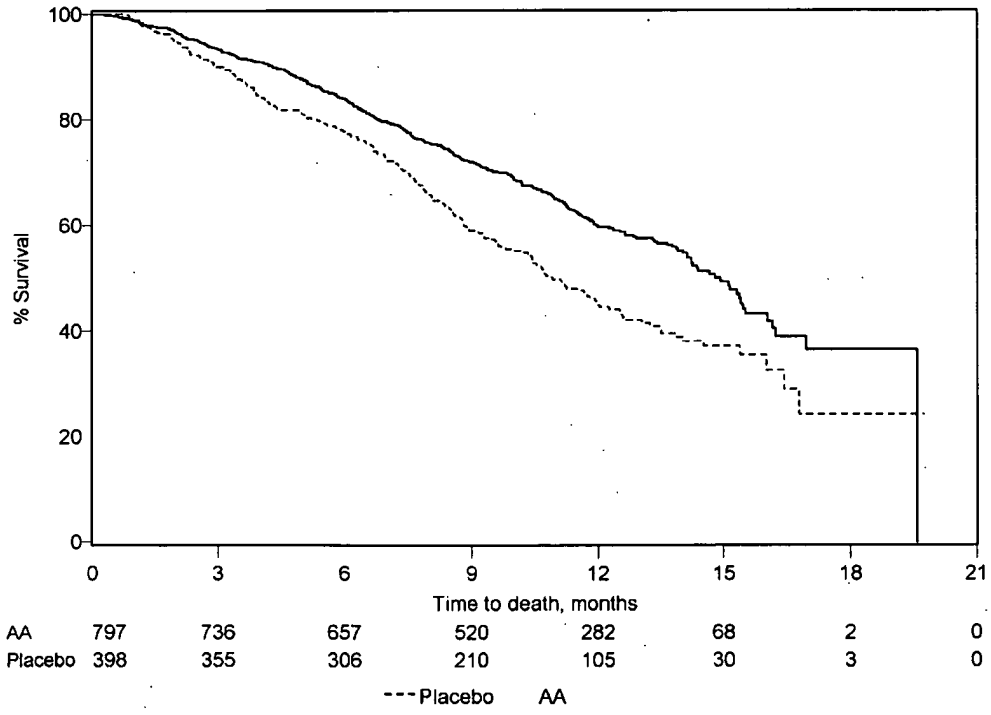
The protocol pre-specified interim analysis was conducted after 552 deaths and showed a statistically significant improvement in overall survival in patients treated with ZYTIGA compared to patients in the placebo arm (Table 3 and Figure 1). An updated survival analysis was conducted when 775 deaths (97% of the planned number of deaths for final analysis) were observed. Results from this analysis were consistent with those from the interim analysis (Table 3).

Table 3: Overall Survival of Patients Treated with Either ZYTIGA or Placebo in Combination with Prednisone (Intent-to-Treat Analysis)

	ZYTIGA (N=797)	Placebo (N=398)
Primary Survival Analysis		
Deaths (%)	333 (42%)	219 (55%)
Median survival (months) (95% CI)	14.8 (14.1, 15.4)	10.9 (10.2, 12.0)
p value [a]	< 0.0001	
Hazard ratio (95% CI) [b]	0.646 (0.543, 0.768)	
Updated Survival Analysis		
Deaths (%)	501 (63%)	274 (69%)
Median survival (months) (95% CI)	15.8 (14.8, 17.0)	11.2 (10.4, 13.1)
Hazard ratio (95% CI) [b]	0.740 (0.638, 0.859)	

[a]P-value is derived from a log-rank test stratified by ECOG performance status score (0-1 vs. 2), pain score (absent vs. present), number of prior chemotherapy regimens (1 vs. 2), and type of disease progression (PSA only vs. radiographic).
[b]Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors ZYTIGA

Figure 1: Kaplan-Meier Overall Survival Curves (Intent-to-Treat Analysis)



AA= ZYTIGA

16 HOW SUPPLIED/STORAGE AND HANDLING

ZYTIGA (abiraterone acetate) 250 mg tablets are white to off-white, oval tablets debossed with AA250 on one side. ZYTIGA 250 mg tablets are available in high-density polyethylene bottles of 120 tablets.

NDC Number 57894-150-12

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) *[see USP controlled room temperature]*.

Based on its mechanism of action, ZYTIGA may harm a developing fetus. Therefore, women who are pregnant or women who may be pregnant should not handle ZYTIGA without protection, e.g., gloves *[see Use in Specific Populations (8.1)]*.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

- Patients should be informed that ZYTIGA and prednisone are used together and that they should not interrupt or stop either of these medications without consulting their physician.
- Patients receiving GnRH agonists should be informed that they need to maintain this treatment during the course of treatment with ZYTIGA and prednisone.
- Patients should be informed that ZYTIGA must not be taken with food and that no food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken. They should be informed that the tablets should be swallowed whole with water. Patients should be informed that taking ZYTIGA with food causes increased exposure and this may result in adverse reactions.
- Patients should be informed that ZYTIGA is taken once daily and prednisone is taken twice daily according to their physician's instructions.
- Patients should be informed that in the event of a missed daily dose of ZYTIGA or prednisone, they should take their normal dose the following day. If more than one daily dose is skipped, patients should be told to inform their physician.
- Patients should be apprised of the common side effects associated with ZYTIGA, including peripheral edema, hypokalemia, hypertension and urinary tract infection. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
- Patients should be advised that their liver function will be monitored using blood tests.
- Patients should be informed that ZYTIGA may harm a developing fetus; thus, women who are pregnant or women who may be pregnant should not handle ZYTIGA without protection, e.g., gloves. Patients should also be informed that it is not known whether

abiraterone or its metabolites are present in semen and they should use a condom if having sex with a pregnant woman. The patient should use a condom and another effective method of birth control if he is having sex with a woman of child-bearing potential. These measures are required during and for one week after treatment with ZYTIGA.

Manufactured by:

Patheon Inc.

Toronto, Canada

Manufactured for:

Centocor Ortho Biotech Inc.

Horsham, PA 19044

Revised: April 2011

PATIENT INFORMATION
ZYTIGA™ (Zye-**tee**-ga)
(abiraterone acetate)
Tablets

Read this Patient information that comes with ZYTIGA before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is ZYTIGA?

ZYTIGA is a prescription medicine that is used along with prednisone. ZYTIGA is used to treat men with castration-resistant prostate cancer (prostate cancer that is resistant to medical or surgical treatments that lower testosterone) that has spread to other parts of the body and who have received treatment with docetaxel.

ZYTIGA is not for use in women or children.

Who should not take ZYTIGA?

Do not take ZYTIGA if you are pregnant or may become pregnant. ZYTIGA may harm your unborn baby.

Women who are pregnant or who may become pregnant should not touch ZYTIGA without protection, such as gloves.

What should I tell my healthcare provider before taking ZYTIGA?

Before you take ZYTIGA, tell your healthcare provider if you:

- have heart problems
- have liver problems
- have a history of adrenal and or pituitary problems
- have any other medical conditions
- plan to become pregnant. See "Who should not take ZYTIGA?"
- are breastfeeding or plan to breastfeed. It is not known if ZYTIGA passes into your breast milk. You and your healthcare provider should decide if you will take ZYTIGA or breastfeed. You should not do both. See "Who should not take ZYTIGA?"

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. ZYTIGA can interact with many other medicines.

You should not start or stop any medicine before you talk with the healthcare provider that prescribed ZYTIGA.

Know the medicines you take. Keep a list of them with you to show to your healthcare provider and pharmacist when you get a new medicine.

How should I take ZYTIGA?

- Take ZYTIGA and prednisone exactly as your healthcare provider tells you.
- Your healthcare provider may change your dose if needed.
- Do not stop taking your prescribed dose of ZYTIGA or prednisone without talking with your healthcare provider first.
- Take ZYTIGA on an empty stomach. **Do not take ZYTIGA with food.** Taking ZYTIGA with food may cause more of the medicine to be absorbed by the body than is needed and this may cause side effects.
- No food should be eaten 2 hours before and 1 hour after taking ZYTIGA.
- Swallow ZYTIGA tablets whole.
- Take ZYTIGA tablets with water.
- Men who are sexually active with a pregnant women must use a condom during and for one week after treatment with ZYTIGA. If their sexual partner may become pregnant, a condom and another form of birth control must be used during and for one week after treatment with ZYTIGA. Talk with your healthcare provider if you have questions about birth control.
- If you miss a dose of ZYTIGA or prednisone, take your prescribed dose the following day. If you miss more than 1 dose, tell your healthcare provider right away.
- Your healthcare provider will do blood tests to check for side effects.

What are the possible side effects of ZYTIGA?

ZYTIGA may cause serious side effects including:

- **High blood pressure (hypertension), low blood potassium levels (hypokalemia) and fluid retention (edema).** Tell your healthcare provider if you get any of the following symptoms:
  - dizziness
  - fast heartbeats
  - feel faint or lightheaded
  - headache
  - confusion
  - muscle weakness
  - pain in your legs
  - swelling in your legs or feet

- **Adrenal problems** may happen if you stop taking prednisone, get an infection, or are under stress.

- **Liver problems.** Your healthcare provider will do blood test to check your liver before treatment with ZYTIGA and during treatment with ZYTIGA.

The most common side effects of ZYTIGA include:

- joint swelling or pain
- muscle aches
- hot flushes
- diarhea
- urinary tract infection
- cough
- irregular heartbeats
- urinate more often than normal
- need to get up at night to urinate
- heartburn
- cold like symptoms

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of ZYTIGA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ZYTIGA?

- Store ZYTIGA at 59°F to 86°F (15°C to 30°C).

Keep ZYTIGA and all medicines out of the reach of children.

General information about ZYTIGA.

Medicines are sometimes prescribed for purposes other than those listed in a patient information leaflet. Do not use ZYTIGA for a condition for which it was not prescribed. Do not give your ZYTIGA to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet summarizes the most important information about ZYTIGA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about ZYTIGA that is written for healthcare professionals.

For more information contact Centocor Ortho Biotech, Inc. at 1-800-457-6399 or *www.Zytiga.com*.

What are the ingredients of ZYTIGA?

Active ingredient: abiraterone acetate

Inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulfate, magnesium stearate and colloidal silicon dioxide.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Patheon Inc.
Toronto, Canada
Manufactured for:
Centocor Ortho Biotech Inc.
Horsham, PA 19044

Issued: April 2011

US005604213A

United States Patent [19]

Barrie et al.

[11] Patent Number: 5,604,213

[45] Date of Patent: Feb. 18, 1997

[54] **17-SUBSTITUTED STEROIDS USEFUL IN CANCER TREATMENT**

[75] Inventors: **Susan E. Barrie**, Kent; **Michael Jarman**, London; **Gerard A. Potter**, Cheshire; **Ian R. Hardcastle**, Sutton, all of Great Britain

[73] Assignee: **British Technology Group Limited**, London, England

[21] Appl. No.: **315,882**

[22] Filed: **Sep. 30, 1994**

Related U.S. Application Data

[63] Continuation-in-part of PCT/GB93/00531 May. 15, 1993.

[30] **Foreign Application Priority Data**

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Nov. 27, 1992	[GB]	United Kingdom	9224880
Sep. 30, 1993	[GB]	United Kingdom	9320132
Jul. 14, 1994	[GB]	United Kingdom	9414192

[51] **Int. Cl.**[6] **A61K 31/58**; C07J 43/00

[52] **U.S. Cl.** **514/176**; 540/95

[58] **Field of Search** 540/95; 514/176

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(List continued on next page.)

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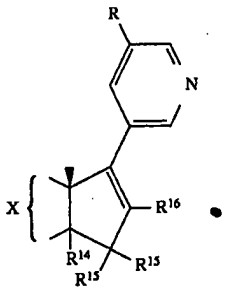
Assistant Examiner—Anthony Bottino
Attorney, Agent, or Firm—Nixon & Vanderhye

[57] **ABSTRACT**

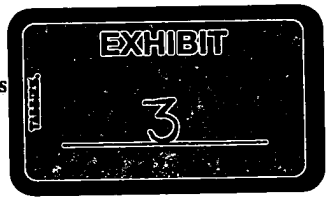
Compounds of the general formula (1)



(1)

wherein X represents the residue of the A, B and C rings of a steroid, R represents a hydrogen atom or an alkyl group of 1 to 4 carbon atoms, R^{14} represents a hydrogen atom and R^{15} represents a hydrogen atom or an alkyl or alkoxy group of 1-4 carbon atoms, or a hydroxy or alkylcarbonyloxy group of 2 to 5 carbon atoms or R^{14} and R^{15} together represent a double bond, and R^{16} represents a hydrogen atom or an alkyl group of 1 to 4 carbon atoms, in the form of the free bases or phannaceutically acceptable acid addition salts, are useful for treatment of androgen-dependent disorders, especially prostatic cancer, and also oestrogen-dependent disorders such as breast cancer.

22 Claims, No Drawings



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17-SUBSTITUTED STEROIDS USEFUL IN CANCER TREATMENT

This specification is a continuation-in-part of PCT Application PCT/GB93/00531, filed Mar. 15, 1993 and which designated the United States of America.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to 17-substituted steroids and their use in the treatment of androgen-dependent and oestrogen-dependent disorders, especially prostatic cancer and breast cancer respectively.

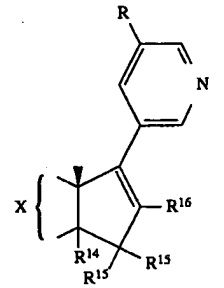
2. Description of the Related Art

The 17α-hydroxylase/C_{17-20} lyase enzyme complex (hereinafter "hydroxylase/lyase") is known to be essential for the biosynthesis of androgens and oestrogens. In the treatment of androgen-dependent disorders, especially prostatic cancer, there is a need for strong inhibitors of hydroxylase/lyase. Certain anti-androgenic steroids are well known, for example Cyproterone acetate (17α-acetoxy-6-chloro-1α, 2α-methylene-4,6-pregnadiene-3,20-dione). Many other steroids have been tested as hydroxylase/lyase inhibitors. See, for example, PCT Specification WO 92/00992 (Schering AG) which describes anti-androgenic steroids having a pyrazole or triazole ring fused to the A ring at the 2,3-position, or European Specifications EP-A 288053 and EP-A 413270 (Merrell Dow) which propose 17β-cyclopropylamino androst-5-en-3β-ol or -4-en-3-one and their derivatives.

SUMMARY OF THE INVENTION

It has now surprisingly been found that steroids lacking a C_{20} side chain and having a 17-(3-pyridyl) ring in its place, together with a 16,17-double bond, are powerful hydroxylase/lyase inhibitors, useful for the above-stated purposes.

According to the invention, there are provided compounds of the general formula



(I)

wherein X represents the residue of the A, B and C rings of asteroid, R represents a hydrogen atom or an alkyl group of 1–4 carbon atoms, R^{14} represents a hydrogen atom, a halogen atom or an alkyl group of 1 to 4 carbon atoms and each of the R^{15} substituents independently represents a hydrogen atom or an alkyl or alkoxy group of 1–4 carbon atoms, a hydroxy group or an alkylcarbonyloxy group of 2 to 5 carbon atoms or together represent an oxo or methylene group or R^{14} and one of the R^{15} groups together represent a double bond and the other R^{15} group represents a hydrogen atom or an alkyl group of 1 to 4 carbon atoms, and R^{16} represents a hydrogen atom, halogen atom, or an alkyl group of 1 to 4 carbon atoms, in the form of the free bases or pharmaceutically acceptable acid addition salts.

The term "steroid" herein includes any compound having the steroidal B and C rings, but in which all or part of the A ring is missing e.g. ring not closed (lacking the 2- or 3-position C-atom or both) or takes the form of a cyclopentane ring. It also includes azasteroids having a ring nitrogen atom in place of a ring carbon atom, especially in the A-ring such as in 4-azasteroids.

In general, the compounds of formula (1) are new and such compounds per se are included in the invention. However, certain of them have been disclosed as intermediates in the synthesis of certain steroids having a 3-pyridyl or 3-pyridonyl group in the 17β-position, see J. Wicha and M. Masnyk, Bulletin of the Polish Academy of Sciences: Chemistry 33 (1–2), 19–27 and 29–37 (1985). The first of these papers says that a 17β-side chain of the form —C=C—C=O or —C=C—C=N favours cardiotonic properties and describes the synthesis of 17β-(3-pyridyl)-14β-androst-4-ene-3β,14-diol, while the second uses this compound to prepare 17β-[3-pyrid-2(1H)onyl]-14β-androst-4-ene-3β,14-diol. Those final compounds differ from those of the present invention by having a saturated D-ting and the paper contains no test results. Insofar as certain compounds within formula (1) are known as intermediates in these syntheses, the invention extends to the compounds only for use in therapy. These are 3β-acetoxy-17-(3-pyridyl)androsta-5,14,16-triene and 3β,15α- and 3β,15β-diacetoxy-17-(3-pyridyl)androsta-5,16-diene. See also J. Wicha. et. al., Heterocycles 20, 231–234 (1983) which is a preliminary communication of the first of the above two papers.

J. Wicha et. al., Bulletin of the Polish Academy of Sciences, Chemistry 32 (1–2), 75–83 (1984) have also described the preparation of 3β-methoxy-17β-(3-pyridyl)androstane and pyridone analogues thereof via the intermediate 3β-methoxy-17-(3-pyridyl)-5α-androst-16-ene. Accordingly, the invention extends to the latter compound only for use in therapy. A preliminary communication of this paper, by J. Wicha and M. Masynk, appeared in Heterocycles 16, 521–524 (1981).

The invention also includes pharmaceutical compositions comprising a compound of formula (1) in association with a pharmaceutically acceptable diluent or carrier. The terminology "pharmaceutical compositions" implies that injectible formulations are sterile and pyrogen-free and thereby excludes any compositions comprising the compound of formula (1) and a non-sterile organic solvent, such as may be encountered in the context of the final stages of preparing these above-mentioned compounds of formula (1) which have been described in the literature but without any therapeutic use being mentioned.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In the compounds of the invention the essential structural features comprise all of:

a 3-pyridyl ring in the 17-position

a ring double bond in the 16,17-position of the D-ring

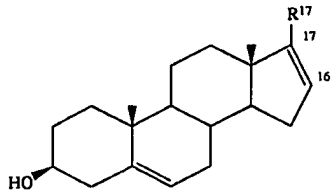
the 18-position methyl group

It is critical that the pyridine nitrogen atom be in the 3-position, not the 2- or 4-position. It is also critical that the pyridine ring be joined directly to the 17-carbon atom. This criticality is demonstrated by tests of inhibiting activity against hydroxylase and lyase (Table 1). The concentration of test compound required to achieve 50% inhibition of the

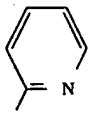
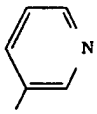
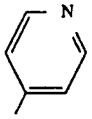
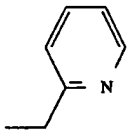
enzyme is far greater for the 2-pyridyl, 4-pyridyl and 2-pyridylmethyl compounds tested than for the 3-pyridyl. The methods of determination were as described in the Examples hereinafter.

TABLE 1

Effect of variations in the 17-substituent on inhibition of hydroxylase and lyase, demonstrating the criticality of the 17-substituent in this invention.



(2)

R^{17}	Type	IC_{50} (μM) Lyase	Hydroylase
	2-Pyridyl (for comparison)	0.13	0.32
	3-pyridyl (present invention)	0.003	0.004
	4-pyridyl (for comparison)	2.0	5.0
	2-picolyl (for comparison)	>10	>10

Note:
all the compounds of formula (2) tested were poor inhibitors of aromatase: IC_{50} >20 μM.

Our modelling of the geometry of the putative transition state of the lyase component of the hydroxylase-lyase enzyme complex, in the putative mechanism of action of the lyase component, suggests that the 16,17-double bond is essential to allow the 3-pyridine ring to adopt the orientation required for co-ordination to the haem group of the hydroxylase-lyase complex.

Elsewhere, the D-ring can have any other simple substituent. Certain simple substituents are defined in connection with the preferred general formula (1), but it will be appreciated that others could be substituted for those of formula (1). In the compounds of formula (1), R^{15} is preferably hydrogen or alkyl of 1 to 3 carbon atoms, R^{16} hydrogen, alkyl of 1 to 3 carbon atoms, fluorine, chlorine, bromine or iodine, and R hydrogen or methyl, in the 5-position of the pyridine ring.

The remainder of the molecule, designated "X" in formula (1), can be of any kind conventional in steroid chemistry or have any other feature known in steroids having anti-androgenic activity, for example the pyrazole or triazole ring, fused to the A ring at the 2- and 3- positions, disclosed in the above-cited Specification WO 92/00992, or oxazole ring fused in the same positions.

By way of example, X can represent the residue of

androstan-3α- or 3β-ol,
androst-5-en-3α- or 3β-ol,
androst-4-en-3-one,
androst-2-ene,
androst-4-ene,
androst-5-ene,
androsta-5,7-dien-3α or 3β-ol,
androsta-1,4-dien-3-one,
androsta-3,5-diene,
estra-1,3,5[10]-triene,
estra-1,3,5[10]-trien-3-ol,
5α-androstan-3-one,
androst-4-ene-3,11-dione,
6-fluoroandrost-4-ene-3-one or
androstan-4-ene-3,6-dione

each of which, where structurally permissible, can be further derivatised in one or more of the following ways:

to form 3-esters, especially 3-alkanoates and -benzoates,
to have one or more carbon to carbon ring double bonds in any of the 5,6-, 6,7-7,8-, 9,11- and 11,12-positions
as 3-oximes
as 3-methylenes
as 3-carboxylates
as 3-nitriles
as 3-nitros
as 3-desoxy derivatives
to have one or more hydroxy, halo, C_{1-4}-alkyl, trifluoromethyl, C_{1-4}-alkoxy, C_{1-4}-alkanoyloxy, benzoyloxy, oxo, methylene or alkenyl substituents in the A, B or C-ring
to be 19-nor.

Preferred C_{1-4}-alkyl and alkoxy groups are methyl and ethoxy.

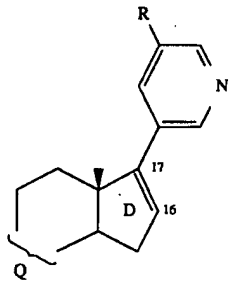
Preferred C_{1-4}-alkanoyloxy groups are acetoxy and propanoyloxy.

Preferred halo groups are fluoro, bromo and chloro and the preferred substitution position is the 6-position.

The substituents include, for instance, 2-fluoro, 4-fluoro, 6-fluoro, 9-fluoro, 3-trifluoromethyl, 6-methyl, 7-methyl, 6-oxo, 7-oxo, 11-oxo, 6-methylene, 11-methylene, 4-hydroxy, 7-hydroxy, 11-hydroxy or 12-hydroxy, each in any appropriate epimeric form, and, subject to structural compatibility (well known in general steroid chemistry), in any combination of two or more such groups.

Compounds which are likely to be unstable are considered excluded from consideration. Such compounds will be evident to steroid chemists. Compounds having esoteric substituents likely to interfere with the stereochemical alignment of the steroid molecule with the enzymes to be inhibited, by virtue of steric or electronic distribution effects, are to be avoided. For example, a 2,3,5,6-tetrafluoro-4-trifluoromethylphenoxy substituent in the 3-position is not recommended. Androst-5-en-3β-ol having such an ether substituent in place of the 3β-hydroxy group has been shown to be a very poor inhibitor for lyase and hydroxylase.

The currently preferred compounds of formula (1) include those which are saturated and unsubstituted at the 11- and 12-positions and which therefore are of the general formula (3):



(3)

wherein Q represents the residue of A, B and C rings of asteroid, and R is a hydrogen atom or an alkyl group of 1–4 carbon atoms.

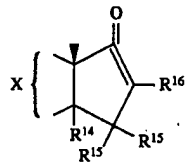
However, 11- and/or 12-substituted compounds are also active. Particularly preferred are 11-oxo and 11β-hydroxy derivatives of compounds of formula (3).

Specifically preferred compounds of the invention comprise
17-(3-pyridyl)androsta-5,16-dien-3β-ol,
17-(3-pyridyl)androsta-3,5,16-triene,
17-(3-pyridyl)androsta-4,16-dien-3-one,
17-(3-pyridyl)estra-1,3,5[10],16-tetraen-3-ol,
17-(3-pyridyl)-5α-androst-16-en-3α-ol
and their acid addition salts and 3-esters.

Other notable compounds of the invention comprise
17-(3-pyridyl)-5α-androst-16-en-3-one,
17-(3-pyridyl)-androsta-4,16-diene-3,11-dione,
17-(3-pyridyl)-androsta-3,5,16-trien-3-ol,
6α- and 6β-fluoro-17-(3-pyridyl)androsta-4,16-dien-3-one
17-(3-pyridyl)androsta-4,16-dien-3,6-dione,
17-[3-(5-methyl pyridyl)]androsta-5,16 dien-3β-ol
3α-trifluoromethyl-17-(3-pyridyl)androsta-16-en-3β-ol
and their acid addition salts and 3-esters.

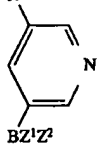
Insofar as certain compounds within formula (1) are known per se and these are compounds which are less easy to prepare than many of the others, a preferred class of compounds of formula (1) is those which do not have a 3β-alkoxy group, a 14,15-double bond or a 15-ester group.

The compounds of formula (1) can be prepared by a method which is in itself novel and inventive. Starting from a 17-oxo compound of general formula (4):



(4)

wherein X, R^{14}, R^{15} and R^{16} are as defined above and any other oxo groups and hydroxy groups in the molecule are first appropriately protected, the method comprises replacing the 17-hydroxy group of compound (4) in its enol form by a leaving group (L) which is capable of being replaced by a 3-pyridyl group in a palladium complex-catalysed cross-coupling reaction with a pyridyl ring-substituted boron compound of formula (5):

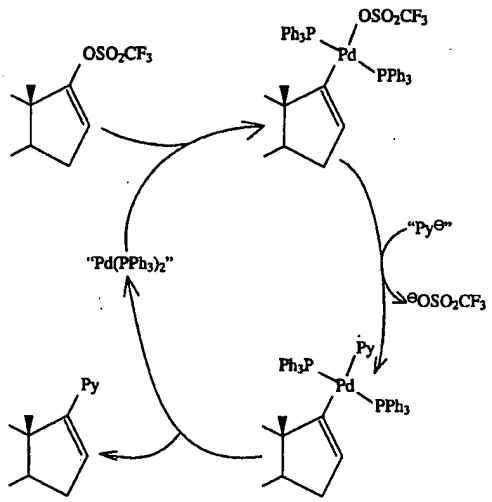


(5)

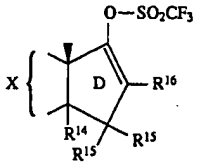
wherein Z^1 and Z^2 independently represent hydroxy or alkoxy or alkyl of 1–4 carbon atoms each, preferably 1–3 carbon atoms, most preferably ethyl or methoxy, or Z^1 and Z^2 together represent an alkylenedioxy group of 2 or 3 carbon atoms and R is as defined above and carrying out said cross-coupling reaction.

The palladium complex-catalysed cross-coupling reaction of the 17-substituted steroid with the boron compound is believed to involve the steps indicated in the following illustrative reaction scheme 1 (Py=3-pyridyl). The pyridyl anionic species is provided by the boron compound.

Scheme 1

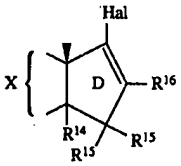


The replacement of the 17-enol group can be, for example, to form a 16,17-ene trifluoromethanesulphonate ("triflate") of formula (6):



(6)

or a 17-iodo or bromo-16,[17]-ene (a "vinyl halide") of formula (7):



(7)

(Hal=I or Br)

Compounds of formula (6) can be prepared by reacting the 17-oxo compound of formula (4) with an enol ester-forming trifluoromethanesulphonic acid derivative such as the anhydride, see S. Cacchi, E. Morera and G. Ortar, Tetrahedron Letters, 25, 4821 (1984). The 17-oxo compound can be considered notionally to exist in the enol form, the reaction being one of esterification of the enol.

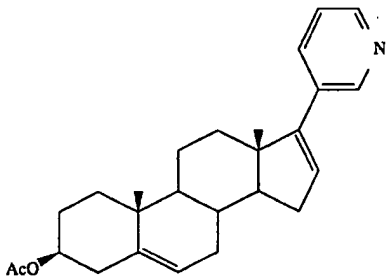
For the preparation of the 17-position derivatives of formula (6) or (7) any necessary protection of other groups in the molecule may be first carried out. For example in the triflate route hydroxyl groups are conveniently protected as their acetates, whilst in the vinyl halide route the 3-oxo group of steroids can be selectively protected as their perfluorotolyl enol ethers, see M. Jarman and R. McCague, J.Chem. Soc. Perkin Trans. 1, 1129 (1987).

Compounds of formula (7) can be prepared by first hydrazinating the 17-oxo compounds of formula (4) by a standard method to form the 17-hydrazone, which is then reacted with bromine or iodine in the presence of an amine or guanidine base, see D. Barton, G. Bashiardes and J. Fourmy, Tetrahedron Letters, 24, 1605 (1983).

The 17-position derivative (whether triflate or vinyl halide) is then reacted with the boron compound of formula (5) using as catalyst a palladium(0) phosphine complex, for example tetrakis(triphenylphosphine)palladium(0), or a palladium (II) phosphine complex which is reducible in situ to a palladium(0) phosphine species, especially bis(triphenylphosphine)palladium (II) chloride.

SUMMARY OF THE INVENTION

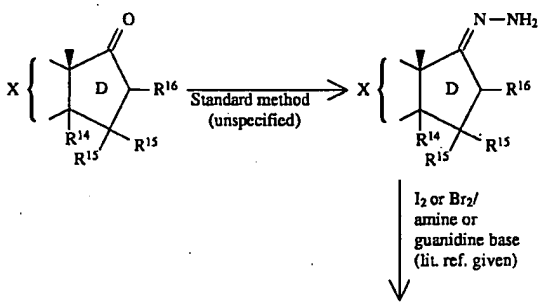
The vinyl halide route, via a compound of formula (7), is particularly well suited to the preparation of 3β-acyloxy-16,17-ene-17-(3-pyridyl) steroids, especially the preferred compound, 3β-acetoxy-17-(3-pyridyl)androsta-5,16-diene, of formula (8):



(8)

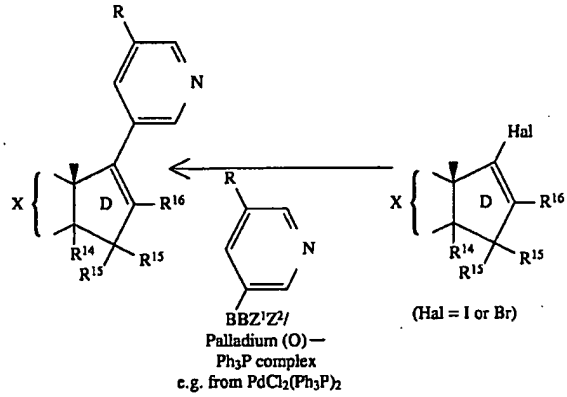
but using the unprotected 3β-hydroxy compound as starting material. By-products can be reduced either (a) by keeping the proportion of organoboron compound (borane) used in the cross-coupling reaction within the range 1.0 to 1.2 equivalents per equivalent of steroid or (b) by crystallising the reaction product of the cross-coupling reaction from a mixture of acetonitrile and methanol. This route via the vinyl iodide intermediate is therefore amenable to large scale synthesis, and is shown in Scheme 2 below.

Scheme 2



-continued

Scheme 2



The principle of this aspect of the invention may be expressed as a method of preparing a 3β-hydroxy- or 3β-(lower acyloxy)-16,17-ene-17-(3-pyridyl)-substituted steroid, wherein the 3β-(lower acyloxy) group of the steroid has from 2 to 4 carbon atoms, which comprises subjecting a 3β-hydroxy-16,17-ene-17-iodo or-bromo steroid to a palladium complex-catalysed cross-coupling reaction with a (3-pyridyl)-substituted borane, in which the pyridine ring is substituted at the 5-position by an alkyl group of 1 to 4 carbon atoms or is unsubstituted thereat, especially with a said borane of formula (5), wherein R is a hydrogen atom or an alkyl group of 1–4 carbon atoms and Z^1 and Z^2 independently represent hydroxy or alkoxy or alkyl or 1–3 carbon atoms each or Z^1 and Z^2 together represent an alkylenedioxy group of 2 or 3 carbon atoms, in a proportion of at least 1.0 equivalent of boron compound per equivalent of steroid, in an organic liquid, which is a solvent for the 3β-hydroxy steroidal reaction product, and optionally esterifying the 3β-hydroxy reaction product to the 3β-acyloxy ester, which method comprises feature (a) or (b) above.

Preferably the vinyl iodide or bromide is unsubstituted in the 14, 15 and 16-positions, in which case it can be prepared from dehydroepiandrosterone (DHEA). In the hydrazination it is preferable to use hydrazine hydrate together with a catalytic amount of a proton provider which is most preferably hydrazine sulfate.

The hydrazone is preferably iodinated with iodine or brominated with bromine in the presence of a strong base such as a tetraalkylguanidine, especially tetramethylguandine which is cheaply and readily available.

In the cross-coupling reaction, the boron compound is preferably a diethylborane or a dimethoxyborane (Z^1=Z^2=Et or OMe). Other boranes include those in which the boron atom is part of a cyclic ether ring e.g. as in Z^1, Z^2=1,2-ethylenedioxy or 1,3-propylenedioxy. In embodiment (a) of this aspect of the invention the proportion of borane added is at least 1.0, but no more than 1.2 equivalents of boron per equivalent of steroid, preferably about 1.1, but in the embodiment (b) a higher proportion is preferred, e.g. from 1.2:1 to 1.5:1 equivalents of boron compound to steroid. The higher proportion will give the better yield of product but also more of the contaminating boron, phosphine and/or palladium compounds. According to embodiment (b), however, these are removed with the acetonitrile solvent. In either embodiment, the palladium compound is a palladium (0) phosphine complex such as tetrakis(triphenylphosphine) palladium (0) or a compound reducible to a palladium (0)

phosphine species, especially bis(triphenylphosphine) palladium (II) chloride. The reaction vessel is preferably purged with an inert gas, especially argon or nitrogen, to minimise the possibility of oxidation with a corresponding redox reduction of palladium to the metallic state.

The cross-coupling reaction is preferably carried out in two phases, one aqueous, one organic. The organic phase comprises an organic solvent for the 3β-hydroxy steroidal reaction product, especially tetrahydrofuran (THF). Other cyclic ethers such as dioxane could be used in place of THF. Preferably, a nucleophilic activator, such as sodium carbonate, is used, in which case it is normally present in the aqueous phase.

After the reaction, inorganic salts can be removed by first adding another organic solvent, preferably diethyl ether, which is a solvent for the organoboron contaminants produced in the reaction product, and miscible with the first-mentioned organic solvent (e.g. THF), but immiscible with water, whereafter the organic, e.g. THF-diethyl ether, phase and water (aqueous phase) can be separated. After this separation, various work-up procedures are operable. In one procedure, particularly suited to embodiment (a), the THF and diethyl ether are removed, e.g. evaporated as a mixture, and the remaining reaction product is washed with a third organic solvent, which can be diethyl ether, preferably cooled to below room temperature, most especially to 10° C. or lower. The third organic solvent is one in which the 3β-hydroxy steroid reaction product has a low solubility and which, importantly, removes the organoboron compound/s (and also the contaminating phosphine and palladium compound/s). Diethyl ether is preferred.

A different work-up procedure, used in embodiment (b), comprises crystallisation from acetonitrile/methanol. Acetonitrile is a preferred crystallisation solvent to keep boron compound as well as palladium compound in solution and is therefore used in an excess over methanol e.g. an excess of at least 5:1 and preferably about 8:1 by volume.

To prepare the 3β-acyloxy (alkylcarbonyloxy) compounds, of which the acetoxy compound is preferred, standard acylating (acyl-esterification) agents such as acetyl, propionyl or butyryl chloride or anhydride can be used. The final esterification product may be crystallised direct from hexane, rather than from ethanol/water followed by hexane. Preferably, the work-up procedure comprises reverse phase chromatography, i.e. using a relatively lipophilic solid phase. In this procedure, the chief by-product, a bis-steroidal compound, is preferentially retained on the solid phase and can be eluted with a good separation from the desired product.

Further compounds of the invention can be prepared by standard steroid to steroid inter-conversion chemistry, so long as the D-ring chemical structure is not affected thereby. If the D-ring structure is likely to be affected, it would usually be necessary to prepare the desired compound de novo, i.e. by choosing the appropriate starting compound of formula (4), protected if necessary, and carrying out the reactions of 17-substitution of the enol and cross-coupling with the boron compound as described above.

By way of example, the 3-esters of asteroid 3-ol with an alkanoic acid of 1 to 6 carbon atoms, or a cycloalkanoic acid or aralkanoic acid such as phenylacetic or phenylpropionic acid, an aroic acid such as benzoic acid, or other simple organic acid such as methanesulphonic acid, can be converted into the 3-ol or the 3-ol to the 3-ester. Other examples of simple conversions which would not affect the D-ring structure are

i) Oppenauer oxidation using cyclohexanone and aluminium isopropoxide to convert 3-hydroxy to 3-oxo steroids and notably $\Delta^{5,6}$-3-hydroxy to $\Delta^{4,5}$-3-oxo steroids;

ii) Wittig olefination to convert oxo groups to methylene groups [D. D. Evans et al., J. Chem. Soc., 4312–4317, (1963)];

iii) Oxidation of Δ^5-3β-hydroxy to Δ^4-3,6-dione steroids using N-methylmorpholine N-oxide and tetra-n-propylammonium perruthenate catalyst [M. Moreno et al., Tetrahedron Letters, 32, 3201–3204, (1991)];

iv) 6-Methylenation of Δ^4-3-oxo steroids using formaldehyde dimethylacetal [K. Annen et al., Synthesis, 34–40 (1982)];

v) Conversion of Δ^4-3-oxo to 4,4-dimethyl-Δ^5-3-oxo, $\Delta^{1,4}$-3-oxo, $\Delta^{1,4,6}$-3-oxo, 7α-methyl-Δ^4-3-oxo, $\Delta^{4,6}$-3-oxo, 6-chloro-$\Delta^{4,6}$-3-oxo, $\Delta^{2,4}$-2,3-isoxazole, 6α-methyl-Δ^4-3-oxo and Δ^4-3-desoxy; Δ^5-3β-ol to 5α-fluoro-6-oxo, 5α,6,6-trifluoro, 6,6-difluoro and 6α-fluoro-Δ^4-3-oxo; and 11-oxo to 11-hydroxy and $\Delta^{9,11}$ steroids [D. Lednicer and L. A. Mitscher, The Organic Chemistry of Drug Synthesis, ls. 2 and 3, Wiley (1980 and 1984)] or

vi) Electrophilic fluorination of steroids using N-fluoropyridinium reagents [T. Umenoto et al., Organic Synthesis 69, 129–143 (1990)].

The compounds of formula (1) may be prepared as salts, e.g. the hydrochloride and converted to the free base form and thereafter to such other conventional pharmaceutically acceptable salts as acetates, citrates and lactates, as may seem appropriate.

The present invention also provides a pharmaceutical composition which comprises a therapeutically effective amount of a compound of the invention, in association with a therapeutically acceptable carrier or diluent. The composition of the invention can, for example, be in a form suitable for parenteral (e.g. intravenous, intramuscular or intracavital), oral, topical or rectal administration. Particular forms of the composition may be, for example, solutions, suspensions, emulsions, creams, tablets, capsules, lipsomes or micro-reservoirs, especially compositions in orally ingestible or sterile injectable form. The preferred form of composition contemplated is the dry solid form, which includes capsules, granules, tablets, pills, boluses and powders. The solid carrier may comprise one or more excipients, e.g. lactose, fillers, disintegrating agents, binders, e.g. cellulose, carboxymethylcellulose or starch or anti-stick agents, e.g. magnesium stearate, to prevent tablets from adhering to tabletting equipment. Tablets, pills and boluses may be formed so as to disintegrate rapidly or to provide slow release of the active ingredient.

The present invention also includes a method of treating androgen- and oestrogen-dependent disorders, especially tumours, and most especially pro static tumours, in the mammalian body, which comprises administering a compound of the invention to a mammalian patient in a therapeutically effective dose, e.g. in the range 0.001–0.04 mmole/kg body weight, preferably 0.001–0.01 mmole/kg, administered daily or twice daily during the course of treatment. This works out (for humans) at 20–800 mg/patient per day. The preferred use is in treating prostatic cancer. Another use is in treating breast cancer.

The following Examples illustrate the invention.

EXAMPLE 1

(a) 3β-Acetoxyandrosta-5,16-dien-17-yl trifluoromethanesulphonate

To a stirred solution of dehydroepiandrosterone-3-acetate (24.8 g, 75 mmol) in dry dichloromethane (500 ml) containing 2,6-di-t-butyl-4-methylpyridine (18.5 g, 90 mmol) was added trifluoromethanesulphonic anhydride (12.6 ml,

75 mmol). After 12 h the mixture was filtered and washed with water (50 ml), dried ($MgSO_4$), and the solvent evaporated. Chromatography, on elution with light petroleum-dichloromethane (6:1), gave firstly androsta-3,5,16-trien-17-yl trifluoromethanesulphonate (3.02 g, 10%) as an oil. ^{1}H-NMR($CDCl_3$) inter alia δ0.99 (3H,s,18-C$\underline{H}_3$), 1.02(3H, s,19-C$\underline{H}_3$), 5.39(1H,m,6-$\underline{H}$), 5.59(1H,m,16-$\underline{H}$), 5.62(1H,m, 3-$\underline{H}$), 5.93(1H,dm,J 9.4 Hz,4-$\underline{H}$); MS m/z 402(M^+). Further elution with light petroleum-dichloromethane (3:1) afforded the title compound (20.1 g, 58%) which crystallised from hexane, m.p. 75°–76° C. ^{1}H-NMR($CDCl_3$) inter alia δ1.00(3H,s, 18-C$\underline{H}_3$), 1.06(3H, s,19-C$\underline{H}_3$), 2.04(3H,s,C$\underline{H}_3CO_2$), 4.59(1H,m,3α-$\underline{H}$), 5.39(1H,dm,J 4.9 Hz,6-$\underline{H}$), 5.58(1H,m,16-$\underline{H}$). Anal. Calcd: C,57.13; H,6.32; S,6.93. Found: C,57.29; H,6.31; S,6.96%.

(b) 3β-Acetoxy-17-(3-pyridyl)androsta-5,16-diene

Diethyl(3-pyridyl)borane (3.38 g, 23 mmol) from Aldrich Chemical Co. Ltd. was added to a stirred solution of 3β-acetoxyandrosta-5,16-dien-17-yl trifluoromethanesulphonate (6.94 g, 15 mmol) in THF (75 ml) containing bis(triphenylphosphine)palladium(II) chloride (0.105 g, 0.15 mmol). An aqueous solution of sodium carbonate (2M, 30 ml) was then added and the mixture heated, with stirring, by an oil bath at 80° C. for 1 h, and allowed to cool. The mixture was partitioned between diethyl ether and water, the ether phase was dried (Na_2CO_3), filtered through a short plug of silica, and concentrated. Chromatography, on elution with light petroleum-diethyl ether (2:1), afforded the title compound (4.95 g, 84%) which crystallised from hexane, m.p. 144°–145° C., ^{1}H-NMR($CDCl_3$) inter alia δ1.05(3H,s, 19-C$\underline{H}_3$), 1.08(3H,s,18-C$\underline{H}_3$), 2.04(3H,s,C$\underline{H}_3CO_2$), 4.60(1H,m,3α-$\underline{H}$), 5.42(1H,dm, J 4.7 Hz,6-$\underline{H}$), 5.99(1H,m, 16-$\underline{H}$), 7.23(1H,m,Py 5-$\underline{H}$) 7.65(1H,m,Py 4-$\underline{H}$), 8.46(1H,m, Py 6-$\underline{H}$), 8.62(1H,m,Py 2-$\underline{H}$). Anal. Calcd: C, 79.75; H, 8.50; N, 3.58. Found: C, 79.78; H, 8.52; N, 3.54%.

EXAMPLE 2

17-(3-Pyridyl)androsta-5,16-dien-3β-ol

To a solution of 3β-acetoxy-17-(3-pyridyl)androsta-5,16-diene (4.90 g, 12.5 mmol) in methanol (50 ml) was added an aqueous solution of sodium hydroxide (10% w/v, 10 ml) and the mixture heated, with stirring, on an oil bath at 80° C. for 5 min., then allowed to cool. The mixture was poured into water, neutralised with hydrochloric acid (1M), rebasified with saturated sodium bicarbonate solution, and extracted with hot toluene (3×100 ml). The toluene extracts were combined, dried (Na_2CO_3), and concentrated. Chromatography, on elution with toluene-diethyl ether (2:1) afforded the title compound (3.45 g, 79%) which crystallised from toluene, mp 228°–229° C.; ^{1}H-NMR ($CDCl_3$ inter alia δ1.05(3H,s,19-C$\underline{H}_3$), 1.07(3H,s,18-C$\underline{H}_3$), 3.54(1H,m,3α-$\underline{H}$), (5.40H,dm,J 5.0 Hz, 6-$\underline{H}$), 5.99(1H,m,16-$\underline{H}$), 7.22(1H, m,Py5-$\underline{H}$), 7.65(1H,m,Py 4-$\underline{H}$), 8.46(1H,m,Py 6-$\underline{H}$), 8.62(1H,m,Py 2-$\underline{H}$). Anal. Calcd: C, 82.47; H, 8.94; N, 4.01. Found: C, 82.40; H, 8.91; N, 3.97%.

EXAMPLE 3

17-(3-Pyridyl)androsta-3,5,16-triene

The method followed that described in Example 1, using in step (b) diethyl(3-pyridyl)borane (0.88 g, 6.0 mmol), androsta-3,5,16-trien-17-yl trifluoromethanesulphonate (2.01 g, 5.0 mmol), prepared in step (a), THF (25 ml), bis(triphenylphosphine)palladium(II) chloride (35 mg, 0.05 mmol), and aqueous sodium carbonate (2M, 10 ml). Chromatography, on elution with dichloromethane, afforded the title compound (1.39 g, 84%) which crystallised from hexane, m.p. 110°–112° C. ^{1}H-NMR ($CDCl_3$) inter alia δ1.02(3H,s,19-C$\underline{H}_3$), 1.07(3H,s,18-C$\underline{H}_3$), 5.44(1H,m,6-$\underline{H}$), 5.61(1H,m,3-$\underline{H}$), 5.95(1H,dm, J 9.8 Hz, 4-$\underline{H}$), 6.01(1H,m, 16-$\underline{H}$), 7.23(1H,m,Py 5-$\underline{H}$), 7.66(1H,m,Py 4-$\underline{H}$), 8.46(1H,m, Py 6-$\underline{H}$), 8.63(1H,m,Py 2-$\underline{H}$); MS m/z 331 (M^+).

EXAMPLE 4

(a) 3-[2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenoxy]androsta-3,5,16-trien-17-yl trifluoromethanesulphonate

The method followed that described in Example 1(a) but using 3-[2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenoxy]androsta-3,5-dien-17-one (5.03 g, 10 mmol), prepared as described in M. Jarman and R. McCague, J. Chem. Soc., Perkin Trans. 1, 1129 (1987), dichloromethane (80 ml), 2,6-di-t-butyl-4-methylpyridine (2.87 g, 14 mmol), and trifluoromethanesulphonic anhydride (1.85 ml, 11 mmol). Chromatography, on elution with light petroleum-dichloromethane (10:1), afforded the title compound (1.93 g, 30%) which crystallised from ethanol, m.p. 106°–107° C. ^{1}H-NMR ($CDCl_3$) inter alia δ1.02(6H,s,18 and 19-C$\underline{H}_3$), 5.16(1H,s,4-$\underline{H}$), 5.28(1H,m,6-$\underline{H}$), 5.59(1H,m,16-$\underline{H}$); MS m/z 634 (M^+).

(b) 3-[2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenoxy]-17-(3-pyridyl)androsta-3,5,16-triene

The method essentially followed that of Example 1(b) but using diethyl(3-pyridyl)borane (0.44 g, 3.0 mmol), 3-[2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenoxy]androsta-3,5,16-trien-17-yl trifluoromethanesulphonate (1.27 g, 2.0 mmol), THF (10 ml), bis(triphenylphosphine)palladium(II) chloride (70 mg, 0.1 mmol), and aqueous sodium carbonate (2M, 5 ml). Chromatography, on elution with light petroleum-diethyl ether (3:1), afforded the title compound (0.82 g, 73%) which crystallised from hexane, m.p. 166.0°–166.5° C. ^{1}H-NMR ($CDCl_3$) inter alia δ1.05(3H,s,19-C$\underline{H}_3$), 1.07(3H,s,18-C$\underline{H}_3$), 5.18(1H,s,4-$\underline{H}$), 5.32(1H,m,6-$\underline{H}$), 6.01(1H,m,16-$\underline{H}$), 7.23(1H,m,Py 5-$\underline{H}$), 7.66(1H,m,Py 4-$\underline{H}$), 8.47(1H,m,Py 6-$\underline{H}$), 8.63(1H,m,Py 2-$\underline{H}$). Anal. Calcd: C, 66.07; H, 5.01; N, 2.49; F, 23.60. Found: C, 65.97; H, 5.02; N, 2.47; F, 23.41%.

(c) 17-(3-Pyridyl)androsta-4,16-dien-3-one

To solution of 3-[2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenoxy]-17-(3-pyridyl)androsta-3,5,16-triene (0.423 g, 0.75 mmol) in THF (5 ml) was added ethanol (5 ml) followed by aqueous hydrochloric acid (1M, 5 ml) and the mixture heated, with stirring, by an oil bath at 65° C. for 48h and allowed to cool. The mixture was poured into water (20 ml), neutralised with aqueous sodium hydroxide (1M), and extracted with diethyl ether (3×30 ml). The ether extracts were combined, dried (Na_2CO_3), and concentrated. Chromatography, on elution with diethyl ether, afforded the title compound (185 mg, 71%) which crystallised from diethyl ether, m.p. 148°–150° C. IR νmax 1674 cm^{-}; ^{1}H-NMR($CDCl_3$) inter alia δ1.07(3H,s,18-C$\underline{H}_3$), 1.24(3H,s,19-C$\underline{H}_3$), 5.76(1H,s,4-$\underline{H}$), 5.99(1H,m,16-$\underline{H}$), 7.23(1H,m,Py 5-$\underline{H}$), 7.64(1H,m,Py 4-$\underline{H}$), 8.47(1H,m,Py 6-$\underline{H}$), 8.62(1H,m,Py 2-$\underline{H}$); MS m/z 347 (M^+).

EXAMPLE 5

(a) 3-Acetoxyestra-1,3,5[10],16-tetraen-17-yl trifluoromethanesulphonate

The method followed that described in Example 1(a), but using oestrone-3-acetate (4.69 g, 15 mmol), dichloromethane (120 ml), 2,6-di-t-butyl-4-methylpyridine (4.00 g, 19.5 mmol), and trifluoromethanesulphonic anhydride (2.8 ml, 16.5 mmol). Chromatography, on elution with light petroleum-dichloromethane (3:1), afforded the title com-

pound (5.21 g, 78%). ^{1}H-NMR($CDCl_3$) inter alia δ1.00(3H, s,18-C$\underline{H}_3$), 2.29(3H,s,C$\underline{H}_3CO_2$), 5.62(1H,m, 16-$\underline{H}$), 6.81(1H,m,ArH), 6.85(1H,m,ArH), 7.26(1H,m,ArH). Anal. Calcd. for $C_{21}H_{23}O_5F_3S_1.½H_2O$: C, 55.62; H, 5.34. Found: C, 55.58: H, 5.14%.

(b) 3-Acetoxy-17-(3-pyridyl)estra-1,3,5[10],16-tetraene

The method followed that described in Example 1(b), but using diethyl(3-pyridyl)borane (1.65 g, 11.2 mmol), 3-acetoxyestra-1,3,5[10],16-tetraen-17-yl trifluoromethanesulphonate (3.56 g, 8.0 mmol), THF (40 ml), bis(triphenylphosphine)palladium(II) chloride (56 mg, 0.08 mmol), and aqueous sodium carbonate (2M, 15 ml).

Chromatography, on elution with light petroleum-diethyl-ether (2:1) afforded the title compound (2.40 g, 80%). ^{1}H-NMR($CDCl_3$) inter alia δ1.04(3H, s,18-C$\underline{H}$), 2.29(3H, s, C$\underline{H}_3CO_2$), 6.03(1H,m,16-$\underline{H}$), 6.82(1H,m,ArH), 6.85(1H,m, ArH), 7.24(1H,m,Py 5-$\underline{H}$), 7.29(1H,m,ArH), 7.69(1H,m,Py 4-$\underline{H}$), 8.48(1H,m,Py 6-$\underline{H}$), 8.65(1H,m,Py 2-$\underline{H}$); MS m/z 373. (M^+).

EXAMPLE 6

17-(3-Pyridyl)estra-1,3,5[10],16-tetraen-3-ol

The method followed that described in Example 2, but using 3-acetoxy-17-(3-pyridyl)estra-1,3,5[10],16-tetraene (2.36 g, 6.3 mmol), methanol (40 ml), aqueous sodium hydroxide (10% w/v, 5 ml), and the mixture was heated at 80° C. for 10 min. Chromatography, on elution with toluene-methanol (8:1), afforded the title compound (1.40 g, 67%) which crystallised from toluene, m.p. 256°–258° C.: ^{1}H-NMR(DMSO) inter alia δ1.01(3H,s,18-C$\underline{H}_3$), 6.15(1H, m,16-$\underline{H}$), 6.47(1H,m,ArH), 6.52(1H,m,ArH), 7.04(1H,m, ArH), 7.35(1H,m,Py 5-$\underline{H}$), 7.79(1H,m,Py 4-$\underline{H}$), 8.45(1H,m, Py 6-$\underline{H}$), 8.62(1H,m,Py 2-$\underline{H}$). Anal. Calcd: C, 83.34; H, 7.60; N, 4.23. Found: C, 83.39; H, 7.78; N, 4.06%.

EXAMPLE 7

3α-Acetoxy-17-(3-pyridyl)-5α-androst-16-ene

The method followed that described in Example 1, using in step (b) diethyl(3-pyridyl)borane (1.41 g, 9.6 mmol), 3α-acetoxy-5α-androst-16-en-17-yl trifluoromethanesulphonate (3.44 g, 7.4 mmol), prepared from the 3α-acetoxy-5α-androstan-17-one by the method of step (a), THF (40 ml), bis(triphenylphosphine)palladium(II) chloride (52 mg, 0.07 mmol), and aqueous sodium carbonate (2M, 15 mmol). Chromatography, on elution with light petroleum-diethyl ether (2:1), afforded the title compound (2.39 g, 82%), ^{1}H-NMR ($CDCl_3$) inter alia δ0.85(3H,s, 19-C$\underline{H}_3$), 1.01(3H,s,18-C$\underline{H}_3$), 2.06(3H,s,C$\underline{H}_3CO_2$), 5.02(1H,m,3β-$\underline{H}$), 6.00(1H,m,16-$\underline{H}$), 7.24(1H,m,Py 5-$\underline{H}$), 7.68(1H,m,Py 4-$\underline{H}$), 8.47(1H,m,Py 6-$\underline{H}$), 8.63(1H,m,Py 2-$\underline{H}$); MS m/z 393 (M^+).

EXAMPLE 8

17-(3-Pyridyl)-5α-androst-16-en-3α-ol

The method followed that described in Example 2, but using 3α-acetoxy-17-(3 -pyridyl)-5α-androst-16-ene (2.33 g, 5.9 mmol), methanol (40 ml), aqueous sodium hydroxide (10% w/v, 8 ml), and the mixture was heated at 80° C. for 20 min. Chromatography, on elution with toluene-methanol (40:1), afforded the title compound (1.62 g, 78%) which crystallised from toluene, m.p. 198°–199° C.; ^{1}H-NMR($CDCl_3$) inter alia. δ0.84(3H,s,19-C$\underline{H}_3$), 1.00(3H,s,18-C$\underline{H}_3$), 4.06(1H,m,3β-$\underline{H}$), 5.97(1H,m,16-$\underline{H}$), 7.21(1H,m,Py 5-$\underline{H}$), 7.64(1H,m,Py 4-$\underline{H}$), 8.45(1H,m,Py 6-$\underline{H}$), 8.61(1H,m,Py 2-$\underline{H}$). Anal. Calcd: C, 82.00; H,9.46; N,3.99. Found: C,81.78; H,9.47; N.3.96%.

EXAMPLE 9

17-(3-Pyridyl)-5α-androst-16-en-3-one

From a solution of 17-(3-Pyridyl)-5α-androst-16-en-3α-ol (1.05 g, 3.0 mmol) in dry toluene (60 ml) and cyclohexanone (10 ml) was distilled off part of the solvent (20 ml) to eliminate moisture. After allowing to cool to 90° C., aluminium isopropoxide (1.02 g, 5.0 mmol) was added and the mixture heated under reflux for 90 min. then allowed to cool. The mixture was diluted with diethyl ether (250 ml), washed with aqueous trisodium citrate (15% w/v; 2×30 ml), dried (Na_2CO_3), and concentrated. Chromatography, on elution with toluene-methanol (40:1), afforded the title compound (0.90 g, 86%) which crystallised from toluene, m.p. 190°–192° C. IR νmax 1713 cm^{-1}; ^{1}H-NMR ($CDCl_3$) inter alia δ1.04 (3H,s,19-C$\underline{H}_3$), 1.07 (3H,s,18-C$\underline{H}_3$), 5.98 (1H,M, 16-$\underline{H}$), 7.22 (1H,m,Py 5-$\underline{H}$), 7.64 (1H,m,Py 4-$\underline{H}$), 8.46 (1H,m,Py 6-$\underline{H}$), 8.61 (1H,m,Py 2-$\underline{H}$); MS m/z 349 (M+). Anal. Calcd: C,82.47; H,8.94; N,4.01. Found: C,82.00; H,8.94; N,3.84[{]jf44a

EXAMPLE 10

a) 3-(tert-Butyldimethylsiloxy)androsta-3,5-diene-11,17-dione

To a solution of adrenosterone (6.0 g, 20 mmol) in dry dichloromethane (120 ml) was added triethylamine (8.4 ml, 60 mmol) followed by tert-butyldimethylsilyl trifluoromethanesulfonate (5.0 ml, 22 mmol) and the mixture stirred at room temperature for 3 h. The dichloromethane was evaporated and the residue redissolved in diethyl ether (100 ml), then allowed to stand for 30 min, after which time an oil separated. The ether phase was decanted off the oil and the solvent evaporated to give the title compound which was used directly in step (b). IR νmax 1705, 1747 cm^{-1}; ^{1}H-NMR($CDCl_3$) inter alia δ0.12 (6H,s,Me_2Si), 0.85 (3H,s,18-C$\underline{H}$3), 0.92 (9H,s,^{t}BuSi) 1.17(3H,s,19-C$\underline{H}_3$), 4.73 (1H,dm, J 6.9 Hz, 6-$\underline{H}$), 5.36 (1H,m,4-$\underline{H}$).

b) 13-(tert-Butyldimethylsiloxy)-11-oxo-androsta-3,5,16-trien-17-yl trifluoromethanesulfonate

To a solution of the product from step (a) in dry THF (100 ml), cooled to −78° C., was added a freshly prepared solution of lithium diisopropylamide [prepared by adding n-butyllithium (1.6M; 13.8 ml, 22 mmol) in hexane to a solution of diisopropylamine (3.1 ml, 22 mmol) in dry THF (25 ml) at −18° C.] and the resultant yellow solution stirred at −78° C. for 30 min. A solution of N-phenyltrifluoromethanesulfonimide (7.15 g, 20 mmol) in dry THF (20 ml) was then added and after an additional 1 h. at −78° C. was allowed to reach ambient temperature. The reaction mixture was poured into water (200 ml) and extracted with diethyl ether (2×200 ml), the combined ether extracts were washed with water (20 ml), dried Na_2CO_3), and concentrated to give the title compound which was used directly in step (c). IR νmax 1710 cm^{-1}, ^{1}H-NMR ($CDCl_3$) inter alia δ0.13 (6H, $^-$S,Me_2Si), 0.92 (9H,s,^{t}Bu Si), 1.35 (6H,2s,18-C$\underline{H}_3$ and 19-C$\underline{H}_3$), 4.75 (1H,m,6-$\underline{H}$) 5.38 (1H,s,4-$\underline{H}$), 5.68 (1H,m,16-H).

c) 3-(tert-Butyldimethylsiloxy)-17-(3-pyridyl)androsta-3,5,16-trien-11-one

The method essentially followed that described in Example 1(b), but using the 13-(tert-butyldimethylsiloxy)-11-oxo-androsta-3,5,16-trien-17-yltrifluoromethanesulfonate from step (b), diethyl (3-pyridyl)borane (3.53 g, 24 mmol), THF (100 ml), bis(triphenylphosphine)palladium (II) chloride (280 mg, 0.4 mmol), and aqueous sodium carbonate (2M;50 ml). Following work-up as described in

Example 1(b) the title compound was obtained, which was used directly in step (d). IR vmax 1705 cm^{-1}, ^{1}H-NMR ($CDCl_3$) inter alia δ0.13 (3H,s,Me_2Si), 0.93 (9H,s,^{t}BuSi), 0.99 (3H,s,18-CH_3), 1.18 (3H,s,19-CH_3), 4.75 (1H,m,6-H) 5.37 (1H,m,4-H), 6.09 (1H,m,16-H), 7.26 (1H,m,Py 5-H), 7.62 (1H,m,Py 4-H), 8.50 (1H,m,Py 6-H), 8.60 (1H,m,Py 2-H). MS m/z 475 (M+).

d) 17-(3-Pyridyl)androsta-4,16-diene-3,11-dione

To a solution of the product from step (c) in wet THF (60 ml) was added a solution of tetrabutylammonium fluoride (1.0M; 10 ml, 10 mmol) in THF, and the mixture stirred at room temperature for 12 h. The mixture was partitioned between diethyl ether and water basified with saturated aqueous sodium bicarbonate, the ether phase isolated, dried (Na_2CO_3), and concentrated. Chromatography, on elution with diethyl ether, afforded the title compound (4.30 g, 60% overall yield from adrenosterone) which crystallised from diethyl ether, m.p. 181°–183° C.

IR vmax 1669, 1703 cm^{-1}; ^{1}H-NMR($CDCl_3$) inter alia δ1.02 (3H,s, 18-CH_3), 1.45 (3H,s,19-CH_3), 5.76 (1 H,s,Py 4-H), 6.08 (1H,m, 16-H) 7.24 (1H,m,Py 5-H), 7.59 (1 H,m,Py 4-H), 8.50 (1H,m,Py 6-H), 8.59 (1H,m,Py 2-H). MS m/z 361 (M+). Anal Calcd: C, 79.74; H,7.53: N,3.88. Found: C,79.58; H,7.57; N,3.89%.

EXAMPLE 11

3-Acetoxy-17-(3-pyridyl)androsta-3,5,16-triene

17-(3-pyridyl)androsta-4,16-dien-3-one (174 mg, 0.50 mmol) was dissolved in isopropenyl acetate (2 ml). p-Toluenesulfonic acid (130 mg, 0.68 mmol) was then added and the mixture heated at 80° C. for 12 h. After allowing to cool the mixture was poured into diethyl ether, washed with saturated aqueous sodium bicarbonate, dried (Na_2CO_3) and concentrated. Chromatography on elution with light petroleum-diethyl ether (1:1), afforded the title Compound (86 mg, 44%), IR vmax 1755 cm^{-1}, ^{1}H-NMR ($CDCl_3$) inter alia δ1.05 (6H,s,18-CH_3 and 19-CH_3), 2.15 (3H,s,$COCH_3$) 5.44 (1H,m,6-H), 5.72(1H,m,4-H), 6.00 (1H,m,16-H), 7.25 (1H, m,Py 5-H), 7.66 (1H,m,Py 4-H), 8.47 (1H,M,Py 6-H), 8.63 (1H,m,Py 2-H). MS m/z 389 (M+).

EXAMPLE 12

6β-Fluoro-17-(3-pyridyl)androsta-4,16-dien-3-one and

EXAMPLE 13

6α-Fluoro-17-(3-pyridyl)androsta-4,16-dien-13-one

To a solution of 3-acetoxy-17-(3-pyridyl)androsta-3,5,16-triene (80 mg, 0.21 mmol) in dry dichloromethane (2 ml) was added N-fluoropyridinium trifluoromethanesulfonate (180 mg, 0.73 mmol) and the mixture heated under reflux for 12 h. The mixture was diluted with diethyl ether (30 ml), washed with dilute aqueous sodium hydroxide (0.5M; 2×5 ml), dried Na_2CO_3), and concentrated. ^{1}H and ^{19}F-NMR at this stage showed the 6-fluorinated products were formed as a 3:2 mixture of the β and α-epimers. Chromatography, on elution with light petroleum-diethyl ether (1:2), gave firstly:-i) the title 6β-epimer (13 mg), 17%) as white crystals, m.p. 167°–169° C. IR vmax 1684 cm^{-1}; ^{1}H-NMR($CDCl_3$) inter alia δ1.11 (3H,s,18-CH_3), 1.37 (3H,s,19-CH_3), 5.06 (1H,dd, $J_{H\text{-}H}$ 2.4 Hz, $J_{H\text{-}F}$ 49 Hz, 6α-H), 5.92 (1H,m,4-H), 6.01 (1H,m,16-H), 7.24 (1H,m,Py 5-H), 7.65 (1H,m,Py 4-H), 8.48 (1H,m,Py 6-H), 8.63 (1H,m,Py 2-H). ^{19}F-NMR δ-165.9 (dt, $J_{H\text{-}F}$ 49 Hz, 6β-F). MS m/z 365 (M+).

Further elution afforded:

ii) The title 6α-epimer (8 mg, 11%) as white crystals, m.p. 167°–169° C., IR vmax 1681 cm^{-1}; ^{1}H-NMR ($CDCl_3$) inter alia δ1.07 (3H,s,18-CH_3), 1.24 (3H,s,19-CH_3), 5.18 (1H, dm,$J_{H\text{-}F}$ 48 Hz, 6β-H), 5.98 (ZH,m,4-H and 16-H), 7.26 (1H,m,Py 5-H), 7.64 (1H,m,Py 4-H), 8.40 (1H, m,Py6-H), 8.63 (1H,m,Py 2-H). ^{19}F-NMR ($CDCl_3$) δ-183.9 (d,$J_{H\text{-}F}$ 48 Hz, 6α-F). MS m/z 365 (M+).

EXAMPLE 14

17-(3-pyridyl)androsta-4,16-dien-3-one (via Oppenauer Oxidation)

This Example illustrates a better method of preparing the compound already prepared in Example 4. The method followed that described in Example 9, but using 17-(3-pyridyl)androsta-5,16-dien-3β-ol (1.05 g, 3.0 mmol). Chromatography, on elution with toluene-methanol (20:1), afforded the title compound (0.85 g, 82%), which crystallised from diethyl ether, m.p. 148°–150° C. Spectroscopic data was identical to that given in Example 4(c). Anal. Calcd: C,82.95; H,8.41; N,4.03 Found: C,83.00; H, 8.50; N,3.99%

EXAMPLE 15

17-(3-pyridyl)androsta-4,16-dien-3-one oxime

To a suspension of 17-(3-pyridyl)androsta-4,16-dien-3-one (125 mg, 0.36 mmol) in ethanol (2 ml) was added hydroxylimine hydrochloride (50 mg, 0.72 mmol), followed by pyridine (0.2 ml), and the mixture heated under reflux for 1 h. then allowed to cool. The solvent was evaporated and the crystalline product triturated under water, collected on a sinter, washed with cold water, and dried in vacuo to give the title oxime as a 1:1 mixture of syn and anti geometric isomers. ^{1}H-NMR ($CDCl_3$) inter alia δ1.06 (3H,s,18-CH_3), 1.13 (3H,s,19-CH_3), 5.75 and 5.80 (1H,2m, isomeric 4-H), 6.01 (1H,m, 16-H), 7.26 (1H,m,Py 5H), 7.68 and 7.88 (1H, 2m, isomeric Py 4-H), 8.48 and 8.53 (1H, 2m, isomeric Py 6-H), 8.63 (1H,m,Py 2-H). MS m/z 362 (M+).

EXAMPLE 16

17-(3-pyridyl)androsta-4,16-diene-3,6-dione

To a solution of 17-(3-pyridyl)androsta-5,16-dien-3β-ol (350 mg, 1.0 mmol) in dry dichloromethane (10 ml) was added N-methylmorphine N-oxide (351 mg, 3.0 mmol) followed by 400 mg of freshly dried and powdered 4 Å molecular sieves and the mixture stirred for 10 min. Tetrapropylammonium perruthenate catalyst (35 mg), 0.1 mmol) was then added, the reaction flask placed in an ultrasonic bath, and the mixture irradiated whilst maintaining the temperature between 20°–30° C. for 2 h. The mixture was then filtered, diluted with diethyl ether, washed with water, dried (Na_2CO_3), and concentrated. Chromatography, on elution with diethyl ether-ether acetate (5:1), afforded the title compound (26 mg, 7%) as white crystals m.p. 210°–212° C. IR vmax 1680 cm^{-1}; ^{1}H-NMR ($CDCl_3$) inter alia δ1.10 (3H,s,18-CH_3), 1.44 (3H,s,19-CH_3), 4.42 (1H,m, enolic 2-H), 5.84 (1H,s,4-H), 6.01 (1H,m,16-H), 7.24 (1H, m,Py 5-H), 7.65 (1H,m,Py 4-H), 8.45 (1H,m,Py 4-H), 8.45 (1H,m,Py 6-H), 8.60 (1H,m,Py 2-H). FAB-MS MS m/z 362 (M+1).

EXAMPLE 17

3α-(Trifluoromethyl)-17-(3-pyridyl)androst-16-en-3β-ol

To a solution of 17-(3-pyridyl)androst-16-en-3-one (100 mg, 0.29 mmol) in THF (2 ml) cooled to 0° C. was added trifluoromethyltrimethylsilane (200 μl, 1.3 mmol) followed

by tetrabutylammonium fluoride trihydrate (10 mg, 0.03 mmol). After 30 min., dilute aqueous hydrochloric acid (1M; 1 ml) was added and the mixture stirred at room temperature for 12 h. The mixture was then basified with saturated aqueous sodium bicarbonate and extracted with diethyl ether. The three extracts were combined, dried (Na_2CO_3), and concentrated. Chromatography, on elution with light petroleum-diethyl ether (1:1), afforded the title compound (87 mg, 73%) which crystallised from toluene, m.p. 192°–193° C. ^{1}H-NMR ($CDCl_3$) inter alia δ0.92 (3H,s,19-CH_3), 1.01 (3H,s,18-CH_3), 5.98 (1H,m,16-H), 7.22 (1H,m, Py 5-H), 7.64 (1H,m,Py 4-H),8.45 (1H,m,Py 6-H), 8.60 (1H,m,Py 2-H); ^{19}F-NMR ($CDCl_3$) δ-79.1 (s,3α-CF_3). MS m/z 419 (M+). Anal. Calcd: C,71.57; H,7.69; N,3.34; F,13.59 Found: C,71.67; H,7.71; N,3.25; F,13.30%.

EXAMPLE 18

(a) Diethyl[3-(5-methylpyridyl)]borane

3-Bromo-5-methylpyridine, which can be prepared as described in the literature, e.g. L. van der Does and H. J. van Hertog, Rec. Trav. Chem. Pays Bas 84, 957–960 (1985) or R. A. Abramovitch and M. Saha, Can. J. Chem. 44, 1765–1771 (1966), is reacted with n-butyllithium, according to the method of M. Terashima et al., Chem. Pharm. Bull. 31, 4573–4577, (1983). The product is treated with triethylborane and then iodine.

(b) 17-[3-(5-Methylpyridyl)]androsta-5,16-dien-3β-ol

Diethyl [3-(5-methylpyridyl)]borane is reacted with 3β-acetoxyandrosta-5,16-dien-17-yl trifluoromethane sulphonate analogously to Example 1(b) and the resulting 3β-acetate is hydrolysed with sodium hydroxide, analogously to Example 2, to yield the title compound.

The following Examples illustrate preparation of compounds of the invention by the vinyl halide route. In Example 19, the 3β-hydroxy product is produced without chromatography, by embodiment (a). In Example 20, the 3β-hydroxy product is not isolated, but in step (d) an impurity has been identified as a 16,17'-bis(steroidal) by-product. This can be removed by reverse phase chromatography, but now that the by-product has been identified, those skilled in the art will be able more easily to identify procedures which will remove it, without the need for chromatography. Further, it is believed that with the higher organoboron:steroid ratios suggested above, the side-reaction leading to this impurity will be reduced.

EXAMPLE 19

(a) Dehydroepiandrosterone-17-hydrazone

To a stirred solution of dehydroepiandrosterone (28.8 g, 0.1 mol) in ethanol (500 ml) was added hydrazine hydrate (19.5 ml, 0.4 mol), followed by a solution of hydrazine sulfate (65 mg, 0.5 mmol) in water (2 ml). After stirring for 3 days the mixture was poured into water (3 liters) to precipitate the product as a white crystalline solid. The product was collected by filtration on a sinter, washed with cold water (2×50 ml), then with Et_2O (50 ml). The product was then dried in vacuo, firstly over silica gel, and finally over P_2O_5, to give the title compound as a white cyrstalline solid (29.6 g, 98%).

Notes

1) The method of Schweder et al., p.202, compound No. 2 therein (using triethylamine) gave a very fine crystalline product which was difficult to filter.

2) The method of Schweder et al. p. 203, compound No. 4 therein (using sodium acetate buffer) gave a slightly lower yield (96%) in trial experiments, whereas the modified procedure used above gave a product amenable for filtration, and in excellent yield (98%).

(b) 17-Iodo-androsta-5,16-dien-3β-ol

To a solution of iodine (53.3 g, 0.21 mol) in THF (2 L), cooled by an ice/water bath to 0° C., was added 1,1,3,3-tetramethylguanidine (63 ml, 57.6 g, 0.50 mol).

A solution of dehydroepiandrosterone-17-hydrazone (30.25 g, 0.10 mol) in THF (750 ml) was then added slowly to the above iodine solution via a transfer needle over about 2 h, whilst maintaining the reaction temperature at 0° C. After all the hydrazone solution was added, the mixture was filtered, and the filtrate concentrated. The remaining oil was then heated on an oil bath for 4 h, allowed to cool, and dissolved in Et20. The Et_2O solution was washed with 1M HCl until the aqueous phase was acidic, washed with 0.5M NaOH, then 1M $Na_2S_2O_3$, and finally with water. The Et_2O phase was separated, dried ($MgSO_4$), and concentrated to give the crude product. Recrystallisation from Et_2O/hexane (3:2) afforded the title compound as off-white crystals (35.8 g, 90%).

(c) 17-(3-Pyridyl)androsta-5,16-dien-3β-ol

Diethyl(3-pyridyl)borane (3.23 g, 22 mmol) from Aldrich Chemical Co. Ltd. was added to a stirred solution of 17-iodo-androsta-5,16-dien-3β-ol (7.96 g, 20 mmol) in THF (120 ml) containing bis(triphenylphosphine)palladium (II) chloride (140 mg, 0.2 mmol). An aqueous solution of sodium carbonate (2M, 50 ml) was then added and the mixture heated, with stirring, by an oil bath at 80° C. for 48 h, and allowed to cool.

The mixture was partitioned between Et_2O and water the organic phase was separated, dried (Na_2CO_3) and twice concentrated from Et_2O by evaporation to remove THF (with Et_2O). The residual solid was then washed with Et_2O (100 ml), the Et_2O solution decanted off, and the remaining white solid recrystallised from toluene (3.94 g, 56%).

Notes

1) The time required for completion needs to be made longer than when using the vinyl triflate (48 h vs 1 h) since it has been found that the vinyl iodide reacts much more slowly.

2) It has been found that a smaller excess of borane than described in the earlier applications (for the vinyl triflate) aids in isolation of product.

3) The work-up procedure enables the product to be isolated without chromatography, thereby enabling scaling up.

(d) 3β-Acetoxy-17-(3-pyridyl)androsta-5,16-diene

To a stirred suspension of finely powdered 17-(3-pyridyl)androsta-5,16-dien-3β-ol (3.50 g, 10 mmol) in dry diethyl ether (150 ml) containing triethylamine (2.3 ml, 16 mmol) and dimethylaminopyridine (0.012 g, 0.1 mmol) was added acetyl chloride (1.0 ml, 14 mmol). The mixture was then stirred at ambient temperature for 12 h, over which time a thick white precipitate of triethylammonium chloride had formed. The mixture was then filtered and the filtrate concentrated to afford the crude product which was recrystallised firstly from ethanol/water (1:1), then finally from hexane to afford the title compound (3.30 g, 84%).

EXAMPLE 20

(a) Dehydroepiandrosterone-17-hydrazone

Into a 10 L round-bottomed flask, fitted with a magnetic stirrer bar, was placed dehydroepiandrosterone (288 g, 1.0 mol) and ethanol (5.0 L). To the resultant stirred solution was added hydrazine hydrate (195 ml, 4.0 mol), followed by a solution of hydrazine sulfate (0.65 g, 0.005 mol) in water

(20 ml) [note: the hydrazine sulfate dissolved in this volume of water at about 40° C.]. After stirring at room temperature for 5 days, water (4.5 L) was added, the mixture poured into water (10 L), and the white crystalline precipitate allowed to settle. The product was collected by filtration on a sinter, washed with cold water (2×500 ml), then with Et_2O (2×500 ml). The product was then dried in vacuo, firstly over silica gel, and finally over P_2O_5, to give the title compound as a whim crystalline solid, mp 204°–206° C. (284.8 g, 94%).

(b) 17-Iodo-androsta-5,16dien-3β-ol

A 10 L round-bottomed flask, fitted with a magnetic stirrer bar, was charged with iodine (156.1 g, 0.615 mol), THF (4.0 L; GPR grade), and Et_2O (2.0 L; BDH specially dried grade). The resultant stirred solution was cooled by an ice/water bath to 0° C. and 1,1,3,3-tetramethylguanidine (188 ml, 173 g, 1.50 mol) was added. A solution of dehydroepiandrosterone-17-hydrazone from step (a) (90.74 g, 0.30 mol) in THF (2.25 L) was then added slowly to the above iodine solution via a canula over about 2 h, whilst maintaining the reaction temperature at 0° C. [note: N_2 is evolved as the hydrazone is added to the iodine solution]. After all the hydrazone solution was added, the mixture was stirred for an additional hour and the precipitate allowed to settle [note: a precipitate of tetramethylguanidium iodide forms during the reaction]. The mixture was then filtered, and the filtrate concentrated to an oil on a rotary evaporator.

This reaction was carried out a total of three times, thus using in total 272.22 g (0.90 mol) of dehydroepiandrosterone-17-hydrazone from step (a). The concentrated residues from the three separate reactions were combined and heated on an oil bath for 4 h, then allowed to cool [note: this converts any 17,17-diiodo by-product into the 17-vinyl iodide product]. This oil was then dissolved in Et_2O (5 L), filtered, and further diluted with additional Et_2O (4 L).

The Et_2O solution was washed with aqueous HCl (1M; 3×500 ml) until the aqueous phase was acidic [note: the ether solution changes colour from brown to yellow when the aqueous phase remains acidified] then finally with water (500 ml). The Et_2O phase was separated, dried ($MgSO_4$), and concentrated to a volume of 3 L, then left to allow the product to crystallise. The yellow crystals were collected by filtration on a sinter, washed with hexane (3×500 ml) and dried under vacuum (335.4 g, 94%). Recrystallisation from ethanol-water (5:1) afforded the product as white crystals (297.3 g, 83%) mp 175°–176° C., lit. mp 173°–174 ° C.

(c) 17-(3-Pyridyl)androsta-5,16-dien-3β-ol

In a 2 L round-bottomed flask, fitted with a magnetic stirrer bar, was placed the steroidal 17-iodo product from step (b) (98.0 g, 0.246 mol) and this was dissolved in THF (1.1 L). The flask was purged with argon and bis(triphenylphosphine)palladium (II) chloride catalyst (1.73 g, 0.0025 mol) was added, followed by diethyl(3-pyridyl)borane (43.35 g, 0.295 mol). To the resultant orange THF solution was added an aqueous solution of sodium carbonate (2M; 500 ml). The flask was fitted with a reflux condenser, and the apparatus purged again with argon. The mixture was then heated under reflux (at about 80° C.) with stirring on a stirrer/heating mantle (Electrothermal MA) for 4 days [note: upon completion of the reaction the organic phase darkens in colour from orange to dark orange/brown], then allowed to cool. This reaction was carried out a total of three times, thus using a total of 294.0 g (0.74 mol) of the steroidal 17-iodo product from step (b).

The reaction mixtures were combined and Et_2O (5 L) added. The organic phase was separated, washed with water (2 L), and left to give a first crop of crystals which were collected by filtration on a sinter. The filtrate was concentrated and the residue redissolved in Et_2O to afford a second crop of crystals. The aqueous phase and washings from the above work-up were extracted with hot toluene (2 L) on a steam bath and concentration of the toluene extracts afforded further product. The combined crude product from the above procedures was then dissolved in the minimum volume of hot methanol, filtered through a plug of "Celite" (Registered Trade Mark) and an equal volume of acetonitrile added to the methanol solution. The acetonitrile/methanol solution was then concentrated to half its original volume on a rotary evaporator and the solution left to crystallise. The resultant white crystals were collected by filtration on a sinter, washed with acetonitrile and dried in vacuo to constant weight (191.1 g, 74%), mp 202°–212° C. A second recrystallisation from toluene-methanol (50:1) afforded the product as white crystals (146.8 g, 57%) mp 214°–218° C., lit. mp 228°–229° C.

(d) 3β-Acetoxy-17-(3-pyridyl)androsta-5,16-diene

The following reaction was carried out in a 500 ml round-bottomed flask, fitted with a magnetic stirrer bar. To a suspension of the steroidal product from step (c) (26.5 g, 0.104 mol) in dry pyridine (200 ml), was added acetic anydride (75 ml) and the mixture stirred at room temperature for 24 h. The pyridine and excess acetic anydride were removed on a rotary evaporator, initially with the water bath at 70° C., and finally at 800° C. for 30 min. The resulting oil was dissolved in Et_2O (500 ml), washed with saturated aqueous $NaHCO_3$ (2×200 ml), dried (Na_2CO_3), and concentrated to an oil which crystallised on standing. ^{1}H-NMR spectroscopy at this stage showed the product contained about 5% of a 16,17'-bi(steroidal) contaminant, 3β-acetoxy-16-(3'-β-acetoxyandrosta-5',16'-dien-17'-yl)-17-(3-pyridyl)androsta-5,16-diene, which originated as a by-product from the coupling reaction of step (c).

The product was therefore further purified by preparative flash chromatography using a 9 cm diameter column, with silica stationary phase (Merck 15111), eluting with dicholoromethane. The by-product eluted first followed by the desired product, although the separation was incomplete. Fractions containing a significant amount of by-product were combined and subjected to further chromatographic purification.

The foregoing reaction and purification procedure was carried out a total of four times, thus using a total of 146 g (0.418 mol) of the steroidal product from step (c).

The product-containing dichloromethane fractions from the chromatographic purification were concentrated and recrystallised from hexane to afford white crystals which were dried in vacuo to constant weight. The total amount of product obtained was 136.0 g (83%).

The dichloromethane fractions containing the least by-product were combined, and following recrystallisation from hexane, afforded the title compound as white crystals with mp 142°–144° C. Analysis showed this material ("A") contained 6.8% w/w of the bis(steroidal) by-product.

A second crop of white crystals ("B") of the product, containing 21.8% w/w of bis(steroidal) by-product (25 g), was obtained.

The two products were purified using reverse phase chromatography. The column was packed with "LiChroprep" (Registered Trade Mark) RP-8 reverse-phase C_8 packing, Art. No. 9324, supplied by E. Merck, Darmstadt, Germany. The course of the chromatography was followed by UV detection at 253 nm, with purity checks by HPLC.

Product "A" (10.17 g) was dissolved in 200 ml. hot acetonitrile and 40 ml. hot methanol, and, after being allowed to cool, the filtrate was applied to a 10 cm. diameter

column containing about 500 g. of the packing. The eluant was 5% 0.05M aqueous ammonium acetate/95% v/v acetonitrile. 7.51 g. of product was recovered in fractions 4–10. Fractions (500 ml) 4–11 contained the product with some impurities, but not the bis-steroidal byproduct. The eluant was changed to 2.5% acetic acid/95.5% v/v acetonitrile and then to 5% acetic acid/95% v/v acetonitrile. A pink colour seen in fractions 16 and 17 evidenced the bis-steroidal by-product. Fraction 18 was colourless. The column can be washed with 100% acetonitrile, for re-use.

Product "B" (1 g) was separated by a similar method except that the product was dissolved initially in 100% acetonitrile and the filtrate applied to a 2 cm. column packed with 100 g. of the solid phase. Excellent separation of the product was achieved with the aqueous ammonium acetate/acetonitrile eluant.

Although, in this Example, the reverse phase column was used in addition to a conventional column, it is clear that the conventional column achieved little separation of the bis-steroidal by-product and it is intended to omit the conventional column in future preparations.

TEST RESULTS

(a) Preparation of testicular material

Human testes were obtained from previously untreated patients undergoing orchidectomy for prostatic cancer. The testes were decapsulated and stored in liquid nitrogen until use. A microsomal preparation was prepared essentially as described by S. E. Barrie et al., J. Steroid Biochem. 6, 1191–5, (1989). The material was then thawed, finely chopped, and homogenised in 0.25M sucrose (5 ml/g wet weight) using a Potter homogeniser. The homogenate was centrifuged at 12000 g for 30 min, and then the microsomes were pelleted by spinning the supernatant at 100,000 g for 1 hr. The pellet was washed by being resuspended in 0.25M sucrose and repelleted. The microsomal pellet was then resuspended in 50 mM sodium phosphate pH 7.4/glycerol (3/1 v/v) and stored in aliquots in liquid nitrogen.

(b) Determination of 17α-hydroxylase

The basic assay mixture was EDTA (0.2 mM), dithiothreitol (DTT; 0.1 mM), NADPH (0.25 mM), glucose 6-phosphate dehydrogenase (G6PDH; 6.25 μg/ml), $MgCl_2$ (1 mM), glucose 6-phosphate (G6P; 10 mM) and the substrate, 3H-progesterone (3 μM) in sodium phosphate (50 mm), pH 7.4. The compounds under test were dissolved in 50% DMSO and the final concentrations of ethanol and DMSO were 1% each. The assay reaction was carded out for 1 hour and was terminated by the addition of 2 vols. of methanol-acetonitrile (2:1) containing approx. 100 μM unlabelled progesterone, 17α-hydroxyprogesterone, androstenedione, testosterone, and 16α-hydroxyprogesterone. The last-mentioned steroid was added as it appeared that the human enzyme was capable of 16α-hydroxylation as well as 17α-hydroxylation.

The separation of the steroids by HPLC was carried out using an "Uptight" guard column packed with 40–63 μm Nucleosil C18 and a 10 cm main column packed with 5 μm Nucleosil C18 and 60% methanol as eluant. The radioactivity in the peaks of interest was monitored on-line by mixing the HPLC effluent 1:1 with Ecoscint A (National Diagnostics) scintillation fluid, containing 25% acetonitrile, and passing the mixture through a Berthold LB506C radiochemical monitor. The hydroxylase activity was measured as the production of 17α-hydroxyprogesterone, androstenedione and testosterone.

(c) Determination of C_{17}–C_{20} lyase

The mixture was the same as described above for the 17α-hydroxylase except that the substrate was ^{3}H-17α-hydroxy- progesterone. The reaction was carried out for 1–2 h. and was stopped by the addition of 2 vols. of methanol/acetonitrile (2/1 containing approx. 100 μM 17α-hydroxyprogesterone, androstenedione and testosterone.

The HPLC separation used for the lyase involved a mini-re-column "Uptight Guard Column" packed with PELL-ODS (pellicular octadecyl silica) and a 10 cm. main column "Apex C18" column packed with 5μ APEX-CAT silica.

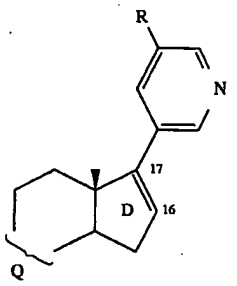
The eluant was 38:12:50 methanol:acetonitrile:water flowing at 1 ml/min. The effluent was mixed 1:1 with Ecoscint A containing 5% methanol and 5% acetonitrile and the radioactivity was measured directly by a Berthold LB506C radiochemical detector. The lyase activity was measured as the production of androstenedione and testosterone.

(d) Calculation of IC_{50}.

The enzyme activity was measured in the presence of at least 4 concentrations of each compound. The data were for the 4-pyridyl and 2-picolyl compounds of Table 1 fitted by linear regression to the Dixon equation (M. Dixon, E.C. Webb, Enzymes, 2nd ed., Academic Press, New York, 1964). Data for all the other compounds were fitted by non-linear regression to the median effect equation of Chou, J. Theoret. Biol. 39, 253–276 (1976). The correlation coefficients were greater than 0.95 except for the compound of Example 1, where it was 0.91. All the assays were carried out with approx. 4 nM enzyme (as calculated from kinetic measurements) except those for Ketoconazole and the 2- and 4-pyridyl and 2-picolyl compounds of Table 1, in which 25 nM lyase and 10 nM hydroxylase were used. The IC_{50} values are dependent on enzyme concentration when the inhibitor binds tightly (all the compounds tested except the 4-pyridyl and 2-picolyl). Results are shown in Table 2 below.

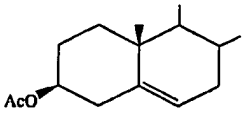
TABLE 2

(a) Confirmation that variations in the A and B rings of compounds of the invention have little effect on inhibition of hydroxylase and lyase.



(3)

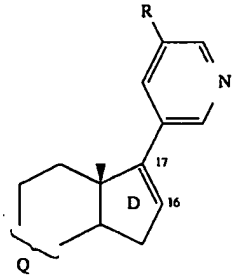
Compounds tested are of formula (3) wherein R = H:

Q	IC_{50} (μM) Lyase	Hydroxylase
	0.0097	0.0130

(Ex. 1)

TABLE 2-continued

(a) Confirmation that variations in the A and B rings of compounds of the invention have little effect on inhibition of hydroxylase and lyase.



(3)

Compounds tested are of formula (3) wherein R = H:

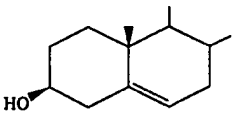
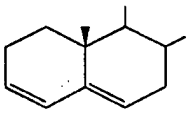
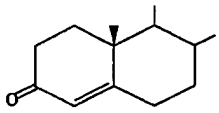
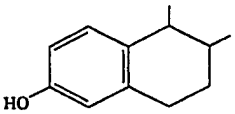
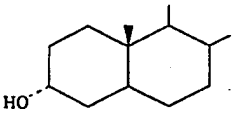
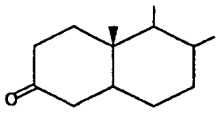
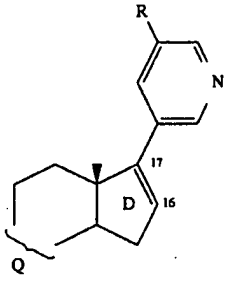
Q	IC_{50} (μM) Lyase	Hydroxylase
 (Ex. 2)	0.0029	0.0040
 (Ex. 3)	0.0056	0.0125
 (Ex. 4)	0.0021	0.0028
 (Ex. 6)	0.0018	0.0026
 (Ex. 8)	0.0025	0.0043
 (Ex. 9)	0.0030	0.0047

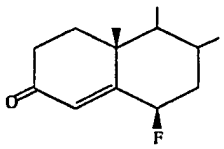
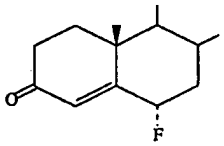
TABLE 2-continued

(a) Confirmation that variations in the A and B rings of compounds of the invention have little effect on inhibition of hydroxylase and lyase.



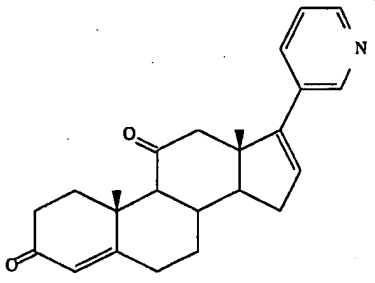
(3)

Compounds tested are of formula (3) wherein R = H:

Q	IC_{50} (μM) Lyase	Hydroxylase
 (Ex. 12)	0.0022	0.0033
 (Ex. 13)	0.0032	0.0053

(b) Confirmation that variation in the C ring of compounds of the invention has little effect on the inhibition of hydroxylase and lyase.

Compound Tested

	IC_{50} (μM) Lyase	Hydroxylase
 (Ex. 10)	0.0025	0.0091

The comparative IC_{50} figures for Ketoconazole are 0.026 against lyase and 0.065 against hydroxylase.

Assay of aromatase activity

Aromatase activity was determined by the method of A. B. Foster et al., J. Med. Chem. 26, 50–54 (1983), using human placental microsomes. For the microsomes used, the Michaelis constant K_m for [1β-^{3}H] androstenedione was 0.039 μM.

The compounds having a pregnenolone-like skeleton in the A and B rings, i.e. 3β-acetoxy-17-(3-pyridyl)androsta-5,16-diene and its 3-alcohol of Examples 1 and 2, had IC_{50}>20 μM. The compound having a progesterone-like skeleton in the A and B rings, i.e. 17-(3-pyridyl)-androsta-4,16-dien-3-one of Example 4 exhibited also aromatase inhibitory activity with IC_{50}=1 μM.

In vivo organ weight and endocrine test in mice

Male HWT mice, 12 weeks old, were treated daily for 2 weeks, with 5 animals per treatment group. The test compounds were the compound of Examples 1 and 4 (as representative of compounds of the invention having the pregenolone-like and progesterone-like skeletons respectively). Ketoconazole was also tested at three different doses. The test compounds were made up in 5% benzyl alcohol, 95% safflower oil, and were given i.p. In addition to an untreated control group of animals, there was also a solvent control group which received the same volume of liquid as the test group (5 ml/kg) but no test compound. All animals were sacrificed 24 hours after the last injection. Blood was collected by cardiac puncture into heparinized tubes, and the plasma used for RIA (radio immunoassay) of testosterone and luteinising hormone. The following organs were removed and weighed: adrenals, prostate, seminal vesicles, testes, kidneys. There was no significant body weight loss in any group of mice during the experiments.

Post mortem examination of the mice revealed oil/white deposits i.p. in those treated with compound of Ex. 1 and white deposits throughout the abdomen in those treated with compound of Ex. 4. In all these mice, all organs looked normal. In Ketoconazole-treated animals, adhesions were found in 2/5,2/5,4/5 of the low/middle/top dose groups. The gut and peritoneal wall seemed to be stuck to the seminal vesicles. The livers were brown in the middle/top dose groups.

The weights of organs found in the animals post mortem are shown in Table 3 below. The reductions in weight of all of the prostate, seminal vesicles, testes and kidneys were much greater for the test compounds of the invention than for Ketoconazole. Ketoconazole caused an increase in adrenal weight at the two highest doses, whereas the compounds of the invention had no significant effect, suggesting that they did not inhibit corticosterone biosynthesis.

TABLE 3

	Mean weight (mg.) ± standard error				
Dose	Adrenals	Prostate	Seminal Vesicles	Testes	Kidneys
		Compound of Ex 1.			
Controls	4.5 ± 0.1	10.1 ± 0.7	189 ± 9	146 ± 3	709 ± 17
Solvent controls	4.5 ± 0.4	10.2 ± 1.3	171 ± 6	122 ± 7	615 ± 28
0.02 mmol/ /kg/day	4.3 ± 0.2	8.0 ± 0.6	136 ± 4	134 ± 4	604 ± 24
0.1 mmol /kg/day	4.0 ± 0.2	5.3 ± 0.3	51 ± 6	95 ± 3	500 ± 8
0.5 mmol /kg/day	4.7 ± 0.2	5.6 ± 0.6	25 ± 2	56 ± 2	449 ± 12

TABLE 3-continued

	Mean weight (mg.) ± standard error				
Dose	Adrenals	Prostate	Seminal Vesicles	Testes	Kidneys
		Compound of Ex. 4			
Controls	4.3 ± 0.4	8.4 ± 0.2	165 ± 18	142 ± 8	652 ± 45
Solvent controls	4.4 ± 0.0	9.2 ± 0.9	152 ± 9	122 ± 8	589 ± 24
0.02 mmol/ /kg/day	4.7 ± 0.2	5.9 ± 0.8	108 ± 4	117 ± 9	599 ± 29
0.1 mmol /kg/day	4.6 ± 0.4	6.4 ± 0.5	61 ± 9	105 ± 5	549 ± 28
0.5 mmol /kg/day	4.9 ± 0.1	4.1 ± 0.5	25 ± 1	59 ± 2	468 ± 15
		Ketoconazole			
Controls	4.2 ± 0.2	8.9 ± 0.8	193 ± 8	145 ± 4	670 ± 12
Solvent controls	4.7 ± 0.4	9.3 ± 1.2	198 ± 18	146 ± 3	615 ± 25
0.01 mmol/ /kg/day	4.8 ± 0.2	9.1 ± 0.8	235 ± 18	141 ± 5	637 ± 22
0.225 mmol /kg/day	6.1 ± 0.3	10.8 ± 1.4	171 ± 5	127 ± 7	574 ± 23
0.5 mmol /kg/day	6.9 ± 0.3	9.3 ± 0.9	179 ± 20	133 ± 6	710 ± 30

The results indicate the inhibition by the components of the invention of androgen and particularly testosterone synthesis. They are confirmed by endocrinological results shown in Table 4.

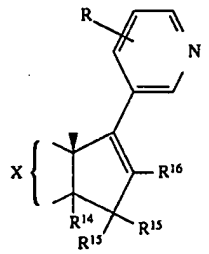
Although the solvent itself produced marked depression of testosterone levels, probably due to stress on the animals, the further decrease resulting from the administration of test compounds was much more marked for the compounds of the invention than for ketoconazole. The rise in LH levels is ascribed to a feedback mechanism associated with depletion of testosterone.

TABLE 4

	Endocrinological Results (Mean ± standard error)	
	Testosterone nM	LH ng/ml
	Compound of Ex. 1	
Controls	9.8 ± 5.6	0.63 ± 0.16
Solvent Controls	2.5 ± 1.2	0.80 ± 0.09
0.02 Mmol/Kg/Day	2.7 ± 0.5	3.4 ± 0.5
0.1 Mmol/Kg/Day	0.2 ± 0.1	2.55 ± 0.45
0.5 Mmol/Kg/Day	0.1 ± 0.0	2.25 ± 0.67
	Compound of Ex. 4	
Control	27.8 ± 11.4	Not determined
Solvent Control	11.0 ± 5.6	Not determined
0.02 Mmol/Kg/Day	4.5 ± 0.3	Not determined
0.1 Mmol/Kg/Day	3.5 ± 1.0	Not determined
0.5 Mmol/Kg/Day	0.4 ± 0.1	Not determined
	Ketoconazole	
Controls	17.3 ± 7.1	0.66 ± 0.05
Solvent Controls	1.3 ± 0.4	0.25 ± 0.13
0.1 Mmol/Kg/Day	0.9 ± 0.2	0.39 ± 0.14
0.225 Mmol/Kg/Day	0.7 ± 0.1	0.75 ± 0.02
0.5 Mmol/Kg/Day	0.4 ± 0.1	0.76 ± 0.03

We claim:

1. A compound of the formula (I)



(I)

wherein X represents the residue of the A, B and C rings of a steroid selected from the group consisting of
androstan-3α- or 3β-ol,
androst-5-en-3α- or 3β-ol,
androst-4-en-3-one,
androst-2-ene,
androst-4-ene,
androst-5-ene,
androsta-5,7-dien-3α or 3β-ol,
androsta-1,4-dien-3-one,
estra-1,3,5[10]-trien-3-ol,
5α-androstan-3-one,
androst-4-ene-3,11-dione,
6-fluoroandrost-4-ene-3-one,
androstan-4-ene-3,6-dione,
each of which, where structurally permissible, can be further derivatised in one or more of the following ways:

to form 3-esters

to have one or more carbon to carbon ring double bonds in any of the 5,6-, 6,7-, 7,8-, 9,11- and 11,12-positions

as 3-oximes

as 3-methylenes

as 3-carboxylates

as 3-nitriles

as 3-nitros

as 3-desoxy derivatives

to have one or more hydroxy, halo, C_{1-4}-alkyl, trifluoromethyl, C_{1-4}-alkoxy, C_{1-4}-alkanoyloxy, benzoyloxy, oxo, methylene or alkenyl substituents in the A, B, or C-ring

to be 19-nor;

R represents a hydrogen atom or an alkyl group of 1–4 carbon atoms;

androsta-3,5-diene,

androsta-3,5-diene-3-ol,

estra-1,3,5[10]-triene and

estra-1,3,5[10]-trien-3-ol,

5α-androstan-3-one:

androst-4-ene-3,11-dione,

6-fluoroandrost-4-ene-3-one,

androstan-4-ene-3,6-dione,

each of which, where structurally permissible, can be further derivatised in one or more of the following ways:

to form 3-esters

to have one or more carbon or carbon ring double bonds in any of the 5,6-, 6,7-, 7,8-, 9,11- and 11,12-positions

as 3-oximes

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as 3-carboxylates

as 3-nitriles

as 3-nitros

as 3-desoxy derivatives

to have one or more hydroxy, halo, C_{1-4}-alkyl, trifluoromethyl, C_{1-4}-alkoxy, C_{1-4}-alkanoyloxy, benzoyloxy, oxo, methylene or alkenyl substituents in the A, B, or C-ring

to be 19-nor;

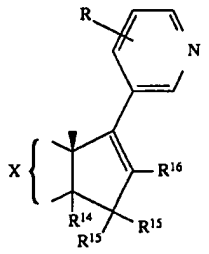
R represents a hydrogen atom or an alkyl group of 1–4 carbon atoms;

R^{14} represents a hydrogen atom, a halogen atom or an alkyl group of 1 to 4 carbon atoms;

each of the R^{15} substituents independently represents a hydrogen atom or an alkyl or alkoxy group of 1–4 carbon atoms, a hydroxy group or an alkylcarbonyloxy group of 2 to 5 carbon atoms or together represent an oxo or methylene group or R^{14} and one of the R^{15} groups together represent a double bond and the other R^{15} group represents a hydrogen atom or an alkyl group of 1 to 4 carbon atoms; and

R^{16} represents a hydrogen atom, halogen atom, or an alkyl group of 1 to 4 carbon atoms, in the form of the free bases or pharmaceutically acceptable acid addition salts, but excluding 3β-acetoxy-17-(3-pyridyl)androsta-5,14,16-triene, 3β,15α- and 3β,15β-diacetoxy-17-(3-pyridyl)androsta-5,16-diene and 3β-methoxy-17-(3-pyridyl-5α-androst-16-ene.

2. A method of treating an androgen-dependent or estrogen-dependent disorder which comprises administering to a patient in a therapeutically effective dose a compound of the formula (1):



(I)

wherein X represents the residue of the A, B and C rings of asteroid selected from the group consisting of
androstan-3α- or 3β-ol,
androst-5-en-3α- or 3β-ol,
androst-4-en-3-one,
androst-2-ene,
androst-4-ene,
androst-5-ene,
androsta-5,7-dien-3α or 3β-ol,
androsta-1,4-dien-3-one,
androsta-3,5-diene,
androsta-3,5-dien-3-ol,
estra-1,3,5[10]-triene and

R^{14} represents a hydrogen atom, a halogen atom or an alkyl group of 1 to 4 carbon atoms;

each of the R^{15} substituents independently represents a hydrogen atom or an alkyl or alkoxy group of 1–4 carbon atoms, a hydroxy group or an alkylcarbonyloxy group of 2 to 5 carbon atoms or together represent an oxo or methylene group or R^{14} and one of the R^{15} groups together represent a double bond and the other R^{15} group represents a hydrogen atom or an alkyl group of 1 to 4 carbon atoms; and

R^{16} represents a hydrogen atom, halogen atom, or an alkyl group of 1 to 4 carbon atoms, in the form of the free bases or pharmaceutically acceptable acid addition salts.

3. A compound according to claim 1, which is saturated and unsubstituted at the 11- and 12-positions.

4.

17-(3-Pyridyl)androsta-5,16-dien-3β-ol,
17-(3-pyridyl)androsta-3,5,16-triene,
17-(3-pyridyl)androsta-4,16-dien-3-one,
17-(3-pyridyl)estra-1,3,5[10],16-tetraen-3-ol,
17-(3-pyridyl)-5α-androst-16-en-3α-ol
and their acid addition salts and 3-esters.

5. A compound according to claim 1 wherein R represents a hydrogen atom.

6.

17-(3-Pyridyl)-5α-androst-16-en-3-one,
17-(3-pyridyl)-androsta-4,16-diene-3,11-dione,
17-(3-pyridyl)-androsta-3,5,16-trien-3-ol,
6α- and 6β-fluoro-17-(3-pyridyl)androsta-4,16-dien-3-one,
17-(3-pyridyl)androsta-4,16-dien-3,6-dione,
3α-trifluoromethyl-17-(3-pyridyl)androst-16-en-3β-ol
and their acid addition salts and 3-esters.

7. 3β-Alkanoyloxy-17-(3-pyridyl)androsta-5,16-dienes in which the alkanoyloxy group has from 2 to 4 carbon atoms.

8. 3β-Acetoxy-17-(3-pyridyl)androsta-5,16-diene.

9. A pharmaceutical composition comprising a compound of claim 1 in association with a pharmaceutically acceptable carrier or diluent.

10. A pharmaceutical composition comprising a compound of claim 3 in association with a pharmaceutically acceptable carrier or diluent.

11. A pharmaceutical composition comprising a compound of claim 1 wherein R represent a hydrogen atom in association with a pharmaceutically acceptable carrier or diluent.

12. A pharmaceutical composition comprising a compound of claim 4 in association with a pharmaceutically acceptable carrier or diluent.

13. A pharmaceutical composition comprising a compound of claim 6 in association with a pharmaceutically acceptable carrier or diluent.

14. A pharmaceutical composition comprising a compound of claim 7 in association with a pharmaceutically acceptable carrier or diluent.

15. A pharmaceutical composition comprising a compound of claim 8 in association with a pharmaceutically acceptable carrier or diluent.

16. A method according to claim 2 wherein the patient has prostatic cancer.

17. A method according to claim 2 wherein the patient has breast cancer.

18. A method according to claim 2 wherein the compound defined in claim 2 is saturated and unsubstituted at the 11- and 12-positions.

19. A method according to claim 2 wherein the compound is selected from the group consisting of:
17-(3-pyridyl)androsta-5,16-dien-3β-ol,
17-(3-pyridyl)androsta-3,5,16-triene,
17-(3-pyridyl)androsta-4,16-dien-3-one,
17-(3-pyridyl)estra-1,3,5[10],16-tetraen-3-ol,
17-(3-pyridyl)-5α-androst-16-en-3α-ol
and their acid addition salts and 3-esters.

20. A method according to claim 2 wherein the compound is a 3β-alkanoyloxy-17-(3-pyridyl)androsta-5,16-diene wherein the alkanoyloxy group has 2 to 4 carbon atoms.

21. A method according to claim 2 wherein the compound is 3β-acetoxy-17-(3-pyridyl)androsta-5,16-diene.

22. An orally ingestible solid composition or a sterile injectable liquid composition comprising respectively a solid or liquid pharmaceutically acceptable carrier or diluent and a compound as defined by general formula (1) of claim 2.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,604,213
DATED : February 18, 1997
INVENTOR(S) : Barrie, et. al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 27, lines 22-46, delete "estra-1,3,5[10]-trien-3-ol ... R represents a hydrogen atom or an alkyl group of 1-4 carbon atoms;"

Column 28, line 52, insert --,-- after "estra-1,3,5[10]-triene"

Column 28, line 52, insert the following after "estra-1,3,5[10]-triene,"

--estra-1,3,5[10]-trien-3-ol,

5α-androstan-3-one,

androst-4-ene-3,11-dione,

6-fluoroandrost-4-ene-3-one,

androstan-4-ene-3,6-dione,

each of which, where structurally permissible, can be further derivatised in one or more of the following ways:

to form 3-esters

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It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

to have one or more carbon to carbon ring double bonds in any of the 5,6-, 6,7-, 7,8-, 9,11- and 11,12-positions

as 3-oximes

as 3-methylenes

as 3-carboxylates

as 3-nitriles

as 3-nitros

as 3-desoxy derivatives

to have one or more hydroxy, halo, C_{1-4}-alkyl, trifluoromethyl, C_{1-4}-alkoxy, C_{1-4}-alkanoyloxy, benzoyloxy, oxo, methylene or alkenyl substituents in the A, B or C-ring

to be 19-nor;

R represents a hydrogen atom or an alkyl group of 1-4 carbon atoms;

Signed and Sealed this

Twenty-seventh Day of February, 2001

Attest:

Nicholas P. Godici

NICHOLAS P. GODICI

Attesting Officer

Acting Director of the United States Patent and Trademark Office

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Patent Number:	5604213		**Application Number:**	08315882	
Issue Date:	02/18/1997		**Filing Date:**	09/30/1994	
Title:	17-SUBSTITUTED STEROIDS USEFUL IN CANCER TREATMENT				
Status:	4th, 8th and 12th year fees paid			**Entity:**	Large
Window Opens:	N/A	**Surcharge Date:**	N/A	**Expiration:**	N/A
Fee Amt Due:	Window not open	**Surchg Amt Due:**	Window not open	**Total Amt Due:**	Window not open
Fee Code:					
Surcharge Fee Code:					
Most recent events (up to 7):	08/13/2008 07/14/2004 07/24/2000	Payment of Maintenance Fee, 12th Year, Large Entity. Payment of Maintenance Fee, 8th Year, Large Entity. Payment of Maintenance Fee, 4th Year, Large Entity. --- End of Maintenance History ---			
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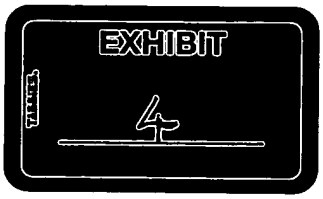

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